Orchard Therapeutics plc

Annual Report and Financial Statements
for the Year Ended 31 December 2020

Registered Number: 11494381

UK FINANCIAL DOCUMENTS

INTRODUCTION AND CONTENTS

Orchard Therapeutics plc (the "Company" or the "Parent Company") is a public limited company incorporated under the laws of England and Wales and is listed on the Nasdaq Global Select Market. This section therefore covers the requirements for being a quoted company under the UK Companies Act 2006, as follows:

COMPANY INFORMATION

Directors	James Geraghty, Chair of the Board of Directors Steven Altschuler (Appointed 3 February 2020) Joanne Beck John Curnutte Marc Dunoyer Jon Ellis Bobby Gaspar Mark Rothera (Resigned 17 March 2020) Charles Rowland Alicia Secor
Secretary	John Ilett
Registered Office	108 Cannon Street London EC4N 6EU United Kingdom
Company Number	11494381
Independent Auditors	PricewaterhouseCoopers LLP 3 Forbury Place 23 Forbury Road Reading, Berkshire, RG1 3JH United Kingdom

CERTAIN NOTE DISCLOSURES RELEVANT TO THE GROUP FINANCIAL STATEMENTS

Basis of Preparation

The consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP"), as permitted by Statutory Instrument 2015 No. 1675, "The Accounting Standards (Prescribed Bodies) (United States of America and Japan) Regulations 2015" and in accordance with the UK Companies Act 2006.

UK Statutory Disclosure Requirements

(i) Monthly average number of people employed

	Number of People	
Group	2020	2019
UK	125	86
Offshore	125	126
Total employees	**250**	**212**

The monthly average number of people employed by the Parent Company (including directors) in 2020 was 8 (2019: 9).

(ii) Employee costs (in thousands)

Group	2020 ($ USD)	2019 ($ USD)
Salaries and bonuses	49,242	41,939
Share-based compensation expense	27,971	19,425
Benefits	3,271	3,202
Defined contribution scheme contributions	1,656	1,263
Social insurance and social security costs	4,951	3,657
Total employee costs	**87,091**	**69,486**

The Parent Company does not have any employees. During fiscal year 2020, the Parent Company had $2,661k in share-based compensation expense associated with equity awards granted to non-executive directors (2019: $1,853k).

(iii) Auditors' remuneration

During the year the Group obtained the following services from the Company's auditors and its associates (in thousands):

Group	2020 ($ USD)	2019 ($ USD)
Fees payable to the Company's auditors and its associates for the audit of the Company and consolidated financial statements for the year ended December 31	1,199	1,455
Audit-related assurance services	222	225
Accounting research tool subscription	3	3
Total fees paid to PricewaterhouseCoopers LLP	**1,424**	**1,683**

PricewaterhouseCoopers LLP ("PwC") has been the Group's auditors beginning in fiscal year 2016. PwC operates procedures to safeguard against the possibility of its objectivity and independence being compromised. This includes PwC's use of quality review partners, consultation with internal compliance teams and carrying out an annual independence procedure. PwC reports to the Audit Committee of the Company's Board of Directors (the "Audit Committee") on matters including independence and non-audit fees on an annual basis. The PwC audit partner changes every five years. The amount charged by the external auditors for the provision of services during the twelve-month period under review is set forth above. The Audit Committee assesses PwC's performance and is comfortable that PwC has operated effectively during the twelve-month period under review. Resolutions to reappoint PwC as the Group's auditors will be put to shareholders at the Company's 2021 Annual General Meeting ("AGM").

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

Report on the audit of the group financial statements

Opinion

In our opinion, Orchard Therapeutics plc's group financial statements:

- give a true and fair view of the state of the group's affairs as at 31 December 2020 and of its loss and cash flows for the year then ended;
- have been properly prepared in accordance with United States Generally Accepted Accounting Principles (US GAAP); and
- have been prepared in accordance with the requirements of the Companies Act 2006.

We have audited the financial statements, included within the Annual Report and Financial Statements (the "Annual Report"), which comprise: the Consolidated Balance Sheet as at 31 December 2020; the Consolidated Statement of Operations and Comprehensive Loss, the Consolidated Statement of Shareholders' Equity, and the Consolidated Statement of Cash Flows for the year then ended; and the notes to the financial statements, which include a description of the significant accounting policies.

Basis for opinion

We conducted our audit in accordance with International Standards on Auditing (UK) ("ISAs (UK)") and applicable law. Our responsibilities under ISAs (UK) are further described in the Auditors' responsibilities for the audit of the financial statements section of our report. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Independence

We remained independent of the group in accordance with the ethical requirements that are relevant to our audit of the financial statements in the UK, which includes the FRC's Ethical Standard, as applicable to listed entities, and we have fulfilled our other ethical responsibilities in accordance with these requirements.

Our audit approach

Overview

Audit scope

- Of the group's seven components, we identified three which, in our view, required an audit of their complete financial information, either due to their size or their risk characteristics. In addition to the full scope audits, specific audit procedures were performed on selected consolidation adjustments made in relation to individually significant balances. This, together with additional procedures performed at group level, gave us the evidence we needed.
- For our opinion of the group as a whole, the components where we performed audit work accounted for 99.7% of group assets and 94.3% of the group loss.

Key audit matters

- Orchard Therapeutics (Europe) Limited Research & Development Tax Credit Receivable
- Impact of Covid-19

Materiality

- Overall materiality: US$8,000,000 (2019: US$8,200,000) based on 5% of loss before tax.
- Performance materiality: US$6,000,000.

continued

The scope of our audit
As part of designing our audit, we determined materiality and assessed the risks of material misstatement in the financial statements.

Capability of the audit in detecting irregularities, including fraud
Irregularities, including fraud, are instances of non-compliance with laws and regulations. We design procedures in line with our responsibilities, outlined in the Auditors' responsibilities for the audit of the financial statements section, to detect material misstatements in respect of irregularities, including fraud. The extent to which our procedures are capable of detecting irregularities, including fraud, is detailed below.

Based on our understanding of the group and industry, we identified that the principal risks of non-compliance with laws and regulations related to patent protection, data privacy, product safety and regulatory compliance, and we considered the extent to which non-compliance might have a material effect on the financial statements. We also considered those laws and regulations that have a direct impact on the preparation of the financial statements such as the Companies Act 2006. We evaluated management's incentives and opportunities for fraudulent manipulation of the financial statements (including the risk of override of controls), and determined that the principal risks were related to misappropriation of cash and potential management bias in accounting estimates. The group engagement team shared this risk assessment with the component auditors so that they could include appropriate audit procedures in response to such risks in their work. Audit procedures performed by the group engagement team and/or component auditors included:

- Discussions with management and internal legal counsel including consideration of known or suspected instances of non-compliance with laws and regulations and fraud.
- Review of minutes of meetings with the Board of Directors.
- Obtaining direct confirmation from the third party contract research organisation (CRO) around the clinical trials being performed on behalf of the company.
- Identifying and testing journal entries, in particular any journal entries posted with unusual account combinations impacting cash.
- Challenging assumptions made by management in their significant accounting estimates, in particular in relation to the research and development tax credit receivable, and balances held with CROs.

There are inherent limitations in the audit procedures described above. We are less likely to become aware of instances of non-compliance with laws and regulations that are not closely related to events and transactions reflected in the financial statements. Also, the risk of not detecting a material misstatement due to fraud is higher than the risk of not detecting one resulting from error, as fraud may involve deliberate concealment by, for example, forgery or intentional misrepresentations, or through collusion.

Key audit matters
Key audit matters are those matters that, in the auditors' professional judgement, were of most significance in the audit of the financial statements of the current period and include the most significant assessed risks of material misstatement (whether or not due to fraud) identified by the auditors, including those which had the greatest effect on: the overall audit strategy; the allocation of resources in the audit; and directing the efforts of the engagement team. These matters, and any comments we make on the results of our procedures thereon, were addressed in the context of our audit of the financial statements as a whole, and in forming our opinion thereon, and we do not provide a separate opinion on these matters.

This is not a complete list of all risks identified by our audit.

The key audit matters below are consistent with last year.

continued

Key audit matter	How our audit addressed the key audit matter
Orchard Therapeutics (Europe) Limited Research & Development Tax Credit Receivable The Company carries out research and development activities and submits tax credit claims under one of two U.K. research and development tax relief programs: either the Small and Medium-sized Enterprises research and development tax relief ("SME") program or the Research and Development Expenditure Credit ("RDEC") program. Each year management evaluates which tax credit program 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 for credit under the program and ultimately be realised. This requires management to make judgments regarding whether the nature of the activities and expenditures will qualify for the tax credit and ultimately be realised based on the allowable reimbursable expense criteria established by the U.K. government. For the year ended 31 December 2020, the Company recorded $21.1 million as a reduction of research and development expense related to these programs and has a related tax credit receivable of $13.3 million as of 31 December 2020. There is therefore a risk that the Company may recognize an excessively high tax credit receivable due to overestimating the amount of eligible expenditure, and that consequently not all of the related tax credit receivable is recoverable.	We have performed the following procedures to address the key audit matter: Obtained management's detailed calculation, reconciled this to the trial balance and tested for mathematical accuracy. Tested a sample of expenses included in the claim, including staff costs, consumables, and subcontractor expenses to underlying supporting documentation. Tested the allocation of a sample of expenses to specific projects, given that this impacts which tax relief programme the expenses are eligible to be claimed under, and also impacts the EU State Aid cap calculation. Confirmed that the correct uplifts and tax rates are being applied in the calculation using HMRC sources. Engaged with our R&D Tax specialists to assess the estimates included within the calculation and the basis on which the claim has been prepared, to ensure this is prepared in compliance with the relevant laws and regulations. No exceptions were identified from the procedures performed.
Impact of Covid-19 The COVID-19 pandemic, and measures taken by governments in order to contain COVID-19 as well as to provide support to businesses, continues to potentially have a significant impact on the operations, liquidity and/or solvency of the group. The COVID-19 outbreak continues to create uncertainty about the long term outlook of most entities as measures taken by governments might change, the disease might spread further, and the economic crisis may deepen, all of which could have an impact on the group. The COVID-19 pandemic has impacted the group operationally with a change to remote working for most employees and a temporary halt in clinical trials during the lockdown period, although these are now resuming in most territories with social distancing restrictions in place. This was reflected in a decrease in certain trial-related costs during 2020 but management consistently budgeted for these to increase before the end of the year as the group adapted to remote working practices.	We considered the impact of COVID-19 on the group's control environment and have performed walkthroughs of the controls in place throughout the pandemic to understand how the group's controls have been adapted as a result of remote working. We have concluded that the control environment has not been significantly impacted by COVID-19 working practices given that the business and staff are well equipped to work remotely in an effective manner. We have also assessed the impact of COVID-19 on the ability of the group to continue as a going concern and deem there not be a significant impact, given the slowdown in expenditure caused by the pandemic, and there being sufficient cash in the group to provide runway into 2023 as a result of the existing cash reserves held, including from the fundraise in February 2021 which generated net proceeds of $144m.

continued

How we tailored the audit scope

We tailored the scope of our audit to ensure that we performed enough work to be able to give an opinion on the financial statements as a whole, taking into account the structure of the group, the accounting processes and controls, and the industry in which it operates.

The group is structured such that the significant majority of its business is comprised of two operating entities - Orchard Therapeutics (Europe) Limited and Orchard Therapeutics North America, both of which were scoped as significant components. We also performed a full scope audit of Orchard Therapeutics plc, as the ultimate parent company in the group. The consolidated financial statements are a consolidation of seven components, comprising the group's operating subsidiaries and centralised functions, which are based throughout the UK, US and Europe. In establishing the overall approach to the audit of the consolidated financial statements, we performed a group scoping assessment, and instructed PwC US to perform a full scope audit over Orchard Therapeutics North America and Orchard Therapeutics plc, along with certain procedures over Orchard Therapeutics (Europe) Limited. We have directed, supervised and reviewed the work of PwC US throughout the audit and maintained regular communication via video calls and email, given that international travel has been prohibited during the Covid-19 pandemic.

Materiality

The scope of our audit was influenced by our application of materiality. We set certain quantitative thresholds for materiality. These, together with qualitative considerations, helped us to determine the scope of our audit and the nature, timing and extent of our audit procedures on the individual financial statement line items and disclosures and in evaluating the effect of misstatements, both individually and in aggregate on the financial statements as a whole.

Based on our professional judgement, we determined materiality for the financial statements as a whole as follows:

Overall group materiality	US$8,000,000.00 (2019: US$8,200,000.00).
How we determined it	5% of loss before tax.
Rationale for benchmark applied	The group is loss making, as expected given its status as an early stage biotech with only two very early stage commercialised products. As such, loss before tax is deemed to be the most appropriate benchmark on which to calculate materiality, as this is the metric on which the group's financial performance is assessed.

For each component in the scope of our group audit, we allocated a materiality that is less than our overall group materiality. The range of materiality allocated across components was $7 million to $7.4 million. Certain components were audited to a local statutory audit materiality that was also less than our overall group materiality.

We use performance materiality to reduce to an appropriately low level the probability that the aggregate of uncorrected and undetected misstatements exceeds overall materiality. Specifically, we use performance materiality in determining the scope of our audit and the nature and extent of our testing of account balances, classes of transactions and disclosures, for example in determining sample sizes. Our performance materiality was 75% of overall materiality, amounting to US$6,000,000.00 for the group financial statements.

In determining the performance materiality, we considered a number of factors – the history of misstatements, risk assessment and aggregation risk and the effectiveness of controls - and concluded that an amount at the upper end of our normal range was appropriate.

continued

We agreed with those charged with governance that we would report to them misstatements identified during our audit above $400,000 (2019: $410,000) as well as misstatements below that amount that, in our view, warranted reporting for qualitative reasons.

Conclusions relating to going concern

Our evaluation of the directors' assessment of the group's ability to continue to adopt the going concern basis of accounting included:

- A review of management's latest cash flow forecast, in which we have assessed the forecasts for reasonableness, understood the planned cash outflows/inflows, considered management's previous ability to forecast accurately and tested the funds received from the February 2021 fundraise to supporting documentation. We also note that a significant proportion of planned expenditure remains under management's control for the foreseeable future, therefore if cash were to run short, management have a number of options under which discretionary expenditure could be reined back.

Based on the work we have performed, we have not identified any material uncertainties relating to events or conditions that, individually or collectively, may cast significant doubt on the group's ability to continue as a going concern for a period of at least twelve months from when the financial statements are authorised for issue.

In auditing the financial statements, we have concluded that the directors' use of the going concern basis of accounting in the preparation of the financial statements is appropriate.

However, because not all future events or conditions can be predicted, this conclusion is not a guarantee as to the group's ability to continue as a going concern.

Our responsibilities and the responsibilities of the directors with respect to going concern are described in the relevant sections of this report.

Reporting on other information

The other information comprises all of the information in the Annual Report other than the financial statements and our auditors' report thereon. The directors are responsible for the other information. Our opinion on the financial statements does not cover the other information and, accordingly, we do not express an audit opinion or, except to the extent otherwise explicitly stated in this report, any form of assurance thereon.

In connection with our audit of the financial statements, our responsibility is to read the other information and, in doing so, consider whether the other information is materially inconsistent with the financial statements or our knowledge obtained in the audit, or otherwise appears to be materially misstated. If we identify an apparent material inconsistency or material misstatement, we are required to perform procedures to conclude whether there is a material misstatement of the financial statements or a material misstatement of the other information. If, based on the work we have performed, we conclude that there is a material misstatement of this other information, we are required to report that fact. We have nothing to report based on these responsibilities.

With respect to the UK Statutory Strategic Report and UK Statutory Directors' Report, we also considered whether the disclosures required by the UK Companies Act 2006 have been included.

Based on our work undertaken in the course of the audit, the Companies Act 2006 requires us also to report certain opinions and matters as described below.

continued

UK Statutory Strategic Report and UK Statutory Directors' Report
In our opinion, based on the work undertaken in the course of the audit, the information given in the UK Statutory Strategic Report and UK Statutory Directors' Report for the year ended 31 December 2020 is consistent with the financial statements and has been prepared in accordance with applicable legal requirements.

In light of the knowledge and understanding of the group and its environment obtained in the course of the audit, we did not identify any material misstatements in the UK Statutory Strategic Report and UK Statutory Directors' Report.

Responsibilities for the financial statements and the audit
Responsibilities of the directors for the financial statements
As explained more fully in the Statement of directors' responsibilities in respect of the financial statements, the directors are responsible for the preparation of the financial statements in accordance with the applicable framework and for being satisfied that they give a true and fair view. The directors are also responsible for such internal control as they determine is necessary to enable the preparation of financial statements that are free from material misstatement, whether due to fraud or error.

In preparing the financial statements, the directors are responsible for assessing the group's ability to continue as a going concern, disclosing, as applicable, matters related to going concern and using the going concern basis of accounting unless the directors either intend to liquidate the group or to cease operations, or have no realistic alternative but to do so.

Auditors' responsibilities for the audit of the financial statements
Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error, and to issue an auditors' report that includes our opinion. Reasonable assurance is a high level of assurance, but is not a guarantee that an audit conducted in accordance with ISAs (UK) will always detect a material misstatement when it exists. Misstatements can arise from fraud or error and are considered material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of these financial statements.

Our audit testing might include testing complete populations of certain transactions and balances, possibly using data auditing techniques. However, it typically involves selecting a limited number of items for testing, rather than testing complete populations. We will often seek to target particular items for testing based on their size or risk characteristics. In other cases, we will use audit sampling to enable us to draw a conclusion about the population from which the sample is selected.

A further description of our responsibilities for the audit of the financial statements is located on the FRC's website at: www.frc.org.uk/auditorsresponsibilities. This description forms part of our auditors' report.

Use of this report
This report, including the opinions, has been prepared for and only for the company's members as a body in accordance with Chapter 3 of Part 16 of the Companies Act 2006 and for no other purpose. We do not, in giving these opinions, accept or assume responsibility for any other purpose or to any other person to whom this report is shown or into whose hands it may come save where expressly agreed by our prior consent in writing.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

Other required reporting

Companies Act 2006 exception reporting

Under the Companies Act 2006 we are required to report to you if, in our opinion:

- we have not obtained all the information and explanations we require for our audit; or
- certain disclosures of directors' remuneration specified by law are not made.

We have no exceptions to report arising from this responsibility.

Other matter

We have reported separately on the company financial statements of Orchard Therapeutics plc for the year ended 31 December 2020 and on the information in the Directors' Remuneration Report that is described as having been audited.

Sam Taylor (Senior Statutory Auditor)
for and on behalf of PricewaterhouseCoopers LLP
Chartered Accountants and Statutory Auditors
Reading

9 April 2021

continued

Report on the audit of the parent company financial statements

Opinion

In our opinion, Orchard Therapeutics plc's parent company financial statements:

- give a true and fair view of the state of the parent company's affairs as at 31 December 2020 and of its loss for the year then ended;
- have been properly prepared in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 102 "The Financial Reporting Standard applicable in the UK and Republic of Ireland", and applicable law); and
- have been prepared in accordance with the requirements of the Companies Act 2006.

We have audited the financial statements, included within the Annual Report and Financial Statements (the "Annual Report"), which comprise: the Parent Company Balance Sheet as at 31 December 2020; the Parent Company Statement of Changes in Equity for the year then ended; and the notes to the financial statements, which include a description of the significant accounting policies.

Basis for opinion

We conducted our audit in accordance with International Standards on Auditing (UK) ("ISAs (UK)") and applicable law. Our responsibilities under ISAs (UK) are further described in the Auditors' responsibilities for the audit of the financial statements section of our report. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Independence

We remained independent of the parent company in accordance with the ethical requirements that are relevant to our audit of the financial statements in the UK, which includes the FRC's Ethical Standard, as applicable to listed entities, and we have fulfilled our other ethical responsibilities in accordance with these requirements.

Our audit approach

Overview

Audit scope

- The audit comprised only the audit of Orchard Therapeutics plc.

Key audit matters

- Impact of Covid-19
- Valuation of investment in Orchard Therapeutics (Europe) Limited

Materiality

- Overall materiality: US$4,546,000.00 (2019: US$5,960,000.00) based on 1% of total assets.
- Performance materiality: US$3,410,000.00.

The scope of our audit

As part of designing our audit, we determined materiality and assessed the risks of material misstatement in the financial statements.

continued

Capability of the audit in detecting irregularities, including fraud
Irregularities, including fraud, are instances of non-compliance with laws and regulations. We design procedures in line with our responsibilities, outlined in the Auditors' responsibilities for the audit of the financial statements section, to detect material misstatements in respect of irregularities, including fraud. The extent to which our procedures are capable of detecting irregularities, including fraud, is detailed below.

Based on our understanding of the parent company and industry, we identified that the principal risks of non-compliance with laws and regulations related to compliance with being a listed company, and we considered the extent to which non-compliance might have a material effect on the financial statements. We also considered those laws and regulations that have a direct impact on the preparation of the financial statements such as the Companies Act 2006. We evaluated management's incentives and opportunities for fraudulent manipulation of the financial statements (including the risk of override of controls), and determined that the principal risks were related to misappropriation of cash. Audit procedures performed by the engagement team included:

- Discussions with management and internal legal counsel including consideration of known or suspected instances of non-compliance with laws and regulations and fraud.
- Review of minutes of meeting with the Board of Directors.
- Identifying and testing journal entries, in particular any journal entries posted with unusual account combinations impacting cash.

There are inherent limitations in the audit procedures described above. We are less likely to become aware of instances of non-compliance with laws and regulations that are not closely related to events and transactions reflected in the financial statements. Also, the risk of not detecting a material misstatement due to fraud is higher than the risk of not detecting one resulting from error, as fraud may involve deliberate concealment by, for example, forgery or intentional misrepresentations, or through collusion.

Key audit matters
Key audit matters are those matters that, in the auditors' professional judgement, were of most significance in the audit of the financial statements of the current period and include the most significant assessed risks of material misstatement (whether or not due to fraud) identified by the auditors, including those which had the greatest effect on: the overall audit strategy; the allocation of resources in the audit; and directing the efforts of the engagement team. These matters, and any comments we make on the results of our procedures thereon, were addressed in the context of our audit of the financial statements as a whole, and in forming our opinion thereon, and we do not provide a separate opinion on these matters.

This is not a complete list of all risks identified by our audit.

Valuation of investment in Orchard Therapeutics (Europe) Limited is a new key audit matter this year. Otherwise, the key audit matters below are consistent with last year.

continued

Key audit matter	How our audit addressed the key audit matter
Impact of Covid-19 The COVID-19 pandemic, and measures taken by governments in order to contain COVID-19 as well as to provide support to businesses, continues to potentially have a significant impact on the operations, liquidity and/or solvency of the company. The COVID-19 outbreak continues to create uncertainty about the long term outlook of most entities as measures taken by governments might change, the disease might spread further, and the economic crisis may deepen, all of which could have an impact on the company.	We considered the impact of COVID-19 on the company's control environment and have performed walkthroughs of the controls in place throughout the pandemic to understand how the company's controls have been adapted as a result of remote working. We have concluded that the control environment has not been significantly impacted by COVID-19 working practices given that the business and staff are well equipped to work remotely in an effective manner. We have also assessed the impact of COVID-19 on the ability of the company to continue as a going concern and deem there not be a significant impact, given the slowdown in expenditure caused by the pandemic, and there being sufficient cash in the group to provide runway into 2023 as a result of the existing cash reserves held, taking into account the fundraise in February 2021 which generated net proceeds of $144m.
Valuation of investment in Orchard Therapeutics (Europe) Limited The parent company holds an investment in its subsidiary, Orchard Therapeutics (Europe) Limited. The reduction in the market capitalisation of Orchard Therapeutics plc, implied by its share price at 31 December 2020 (and the fact that this below the carrying value of the investment) is an indicator of potential impairment of the investment. Because of the uncertainties involved in a value in use calculation management assessed the market capitalisation to be representative of the fair value less costs of disposal of the investment and therefore the realisable value. As a result an impairment of $792.8m has been recorded.	We have performed the following procedures over the impairment assessment which management have prepared: – Assessed management's impairment model and calculation for compliance with UK GAAP (FRS 102). – Corroborated the inputs to the model and validated these to external sources or our audit testing performed in other areas. – Recalculated the impairment to be recognised in the year as the excess of the carrying value of the investment over its recoverable amount, which is determined using a fair value less costs to sell method. – Reviewed the disclosures in the financial statements. No exceptions have been noted from the work performed.

continued

How we tailored the audit scope
We tailored the scope of our audit to ensure that we performed enough work to be able to give an opinion on the financial statements as a whole, taking into account the structure of the parent company, the accounting processes and controls, and the industry in which it operates.

Although the parent company is a UK company, most procedures have been performed by PwC US as component auditors. We instructed PwC US to report on the special purpose financial information of the parent company prepared under US GAAP, and we have performed testing on the adjustments posted by management to prepare the parent company financial statements under FRS 102.

Materiality
The scope of our audit was influenced by our application of materiality. We set certain quantitative thresholds for materiality. These, together with qualitative considerations, helped us to determine the scope of our audit and the nature, timing and extent of our audit procedures on the individual financial statement line items and disclosures and in evaluating the effect of misstatements, both individually and in aggregate on the financial statements as a whole.

Based on our professional judgement, we determined materiality for the financial statements as a whole as follows:

Overall parent company materiality	US$4,546,000.00 (2019: US$5,960,000.00).
How we determined it	1% of total assets
Rationale for benchmark applied	We believe that total assets is the primary measure used by the shareholders in assessing the performance and position of the parent company and reflects the parent company's principal activity as a holding company.

We use performance materiality to reduce to an appropriately low level the probability that the aggregate of uncorrected and undetected misstatements exceeds overall materiality. Specifically, we use performance materiality in determining the scope of our audit and the nature and extent of our testing of account balances, classes of transactions and disclosures, for example in determining sample sizes. Our performance materiality was 75% of overall materiality, amounting to US$3,410,000.00 for the parent company financial statements.

In determining the performance materiality, we considered a number of factors – the history of misstatements, risk assessment and aggregation risk and the effectiveness of controls – and concluded that an amount at the upper end of our normal range was appropriate.

We agreed with those charged with governance that we would report to them misstatements identified during our audit above $243,000 (2019: $410,000) as well as misstatements below that amount that, in our view, warranted reporting for qualitative reasons.

Conclusions relating to going concern
Our evaluation of the directors' assessment of the parent company's ability to continue to adopt the going concern basis of accounting included:

- A review of management's latest cash flow forecast, in which we have assessed the forecasts for reasonableness, understood the planned cash outflows/inflows, considered management's previous ability to forecast accurately and tested the funds received from the February 2021 fundraise to supporting documentation. We also note that a significant proportion of planned expenditure remains under management's control for the foreseeable future, therefore if cash were to run short, management have a number of options under which discretionary expenditure could be reined back.

continued

Based on the work we have performed, we have not identified any material uncertainties relating to events or conditions that, individually or collectively, may cast significant doubt on the parent company's ability to continue as a going concern for a period of at least twelve months from when the financial statements are authorised for issue.

In auditing the financial statements, we have concluded that the directors' use of the going concern basis of accounting in the preparation of the financial statements is appropriate.

However, because not all future events or conditions can be predicted, this conclusion is not a guarantee as to the parent company's ability to continue as a going concern.

Our responsibilities and the responsibilities of the directors with respect to going concern are described in the relevant sections of this report.

Reporting on other information

The other information comprises all of the information in the Annual Report other than the financial statements and our auditors' report thereon. The directors are responsible for the other information. Our opinion on the financial statements does not cover the other information and, accordingly, we do not express an audit opinion or, except to the extent otherwise explicitly stated in this report, any form of assurance thereon.

In connection with our audit of the financial statements, our responsibility is to read the other information and, in doing so, consider whether the other information is materially inconsistent with the financial statements or our knowledge obtained in the audit, or otherwise appears to be materially misstated. If we identify an apparent material inconsistency or material misstatement, we are required to perform procedures to conclude whether there is a material misstatement of the financial statements or a material misstatement of the other information. If, based on the work we have performed, we conclude that there is a material misstatement of this other information, we are required to report that fact. We have nothing to report based on these responsibilities.

With respect to the UK Statutory Strategic Report and UK Statutory Directors' Report, we also considered whether the disclosures required by the UK Companies Act 2006 have been included.

Based on our work undertaken in the course of the audit, the Companies Act 2006 requires us also to report certain opinions and matters as described below.

UK Statutory Strategic Report and UK Statutory Directors' Report

In our opinion, based on the work undertaken in the course of the audit, the information given in the UK Statutory Strategic Report and UK Statutory Directors' Report for the year ended 31 December 2020 is consistent with the financial statements and has been prepared in accordance with applicable legal requirements.

In light of the knowledge and understanding of the parent company and its environment obtained in the course of the audit, we did not identify any material misstatements in the UK Statutory Strategic Report and UK Statutory Directors' Report.

Directors' Remuneration

In our opinion, the part of the Directors' Remuneration Report to be audited has been properly prepared in accordance with the Companies Act 2006.

continued

Responsibilities for the financial statements and the audit

Responsibilities of the directors for the financial statements

As explained more fully in the Statement of directors' responsibilities in respect of the financial statements, the directors are responsible for the preparation of the financial statements in accordance with the applicable framework and for being satisfied that they give a true and fair view. The directors are also responsible for such internal control as they determine is necessary to enable the preparation of financial statements that are free from material misstatement, whether due to fraud or error.

In preparing the financial statements, the directors are responsible for assessing the parent company's ability to continue as a going concern, disclosing, as applicable, matters related to going concern and using the going concern basis of accounting unless the directors either intend to liquidate the parent company or to cease operations, or have no realistic alternative but to do so.

Auditors' responsibilities for the audit of the financial statements

Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error, and to issue an auditors' report that includes our opinion. Reasonable assurance is a high level of assurance, but is not a guarantee that an audit conducted in accordance with ISAs (UK) will always detect a material misstatement when it exists. Misstatements can arise from fraud or error and are considered material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of these financial statements.

Our audit testing might include testing complete populations of certain transactions and balances, possibly using data auditing techniques. However, it typically involves selecting a limited number of items for testing, rather than testing complete populations. We will often seek to target particular items for testing based on their size or risk characteristics. In other cases, we will use audit sampling to enable us to draw a conclusion about the population from which the sample is selected.

A further description of our responsibilities for the audit of the financial statements is located on the FRC's website at: www.frc.org.uk/auditorsresponsibilities. This description forms part of our auditors' report.

Use of this report

This report, including the opinions, has been prepared for and only for the parent company's members as a body in accordance with Chapter 3 of Part 16 of the Companies Act 2006 and for no other purpose. We do not, in giving these opinions, accept or assume responsibility for any other purpose or to any other person to whom this report is shown or into whose hands it may come save where expressly agreed by our prior consent in writing.

Other required reporting

Companies Act 2006 exception reporting

Under the Companies Act 2006 we are required to report to you if, in our opinion:

- we have not obtained all the information and explanations we require for our audit; or
- adequate accounting records have not been kept by the parent company, or returns adequate for our audit have not been received from branches not visited by us; or
- certain disclosures of directors' remuneration specified by law are not made; or
- the financial statements and the part of the Directors' Remuneration Report to be audited are not in agreement with the accounting records and returns.

We have no exceptions to report arising from this responsibility.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

Other matter

We have reported separately on the group financial statements of Orchard Therapeutics plc for the year ended 31 December 2020.

Sam Taylor (Senior Statutory Auditor)
for and on behalf of PricewaterhouseCoopers LLP
Chartered Accountants and Statutory Auditors
Reading

9 April 2021

STATEMENT OF DIRECTORS' RESPONSIBILITIES IN RESPECT OF THE FINANCIAL STATEMENTS

The directors are responsible for preparing the Annual Report and the financial statements in accordance with applicable law and regulation.

Company law requires the directors to prepare financial statements for each financial year. Under that law the directors have prepared the group financial statements in accordance with United States Generally Accepted Accounting Principles (US GAAP) and parent company financial statements in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 102 "The Financial Reporting Standard applicable in the UK and Republic of Ireland", and applicable law).

Under company law, directors must not approve the financial statements unless they are satisfied that they give a true and fair view of the state of affairs of the group and parent company and of the profit or loss of the group for that period. In preparing the financial statements, the directors are required to:

- select suitable accounting policies and then apply them consistently;
- state whether applicable accounting policies as issued by United States Generally Accepted Accounting Principles (US GAAP) have been followed for the group financial statements and United Kingdom Accounting Standards, comprising FRS 102 have been followed for the parent company financial statements, subject to any material departures disclosed and explained in the financial statements;
- make judgements and accounting estimates that are reasonable and prudent; and
- prepare the financial statements on the going concern basis unless it is inappropriate to presume that the group and parent company will continue in business.

The directors are also responsible for safeguarding the assets of the group and parent company and hence for taking reasonable steps for the prevention and detection of fraud and other irregularities.

The directors are responsible for keeping adequate accounting records that are sufficient to show and explain the group's and parent company's transactions and disclose with reasonable accuracy at any time the financial position of the group and parent company and enable them to ensure that the financial statements and the Directors' Remuneration Report comply with the Companies Act 2006.

The directors are responsible for the maintenance and integrity of the parent company's website. Legislation in the United Kingdom governing the preparation and dissemination of financial statements may differ from legislation in other jurisdictions.

STATEMENT OF DIRECTORS' RESPONSIBILITIES IN RESPECT OF THE FINANCIAL STATEMENTS

continued

Directors' confirmations

In the case of each director in office at the date the directors' report is approved:

- so far as the director is aware, there is no relevant audit information of which the group's and parent company's auditors are unaware; and
- they have taken all the steps that they ought to have taken as a director in order to make themselves aware of any relevant audit information and to establish that the group's and parent company's auditors are aware of that information.

UK STATUTORY STRATEGIC REPORT

Introduction

The directors of Orchard Therapeutics plc (which together may be referred to as "Company", "Orchard", "we", "us", or "our") present their UK Statutory Strategic Report on the Group and the audited consolidated financial statements for the year ended 31 December 2020. Orchard also filed with the U.S. Securities and Exchange Commission (the "SEC") its Annual Report on Form 10-K for the year ended 31 December 2020, which may contain additional disclosures regarding some of the matters discussed in this report.

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.

To date, we have financed our operations primarily with proceeds from the sale of American Depositary Shares (ADSs) in our IPO and follow-on offering, proceeds from the sale of convertible preferred shares, reimbursements from our research agreement with the University of California Los Angeles and, following transfer of the adenosine deaminase severe combined immunodeficiency (ADA-SCID) research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine ("CIRM"), and our Credit Facility.

On February 27, 2020, we entered into a Sales Agreement with Cowen and Company, LLC, as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. As of December 31, 2020, we have not sold any shares under the Sales Agreement.

Through December 31, 2020, we have received net proceeds of $335.2 million from the sale of ADSs in our initial public offering and follow-on offering, net proceeds of $283.4 million from sales of convertible preferred shares, $24.5 million in net proceeds from our Credit Facility, receipts associated with our United Kingdom research and development tax credit of $33.9 million, proceeds from share issuances from employee equity plans of $7.1 million, and reimbursement of $8.2 million from our agreement with CIRM, which was formerly a subcontract agreement with UCLA. As of December 31, 2020, we had cash, cash equivalents, and marketable securities of $191.9 million, excluding restricted cash.

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 (the "Private Placement"). The Private Placement resulted in net proceeds to us of approximately $144.0 million after deducting placement agent fees. 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.

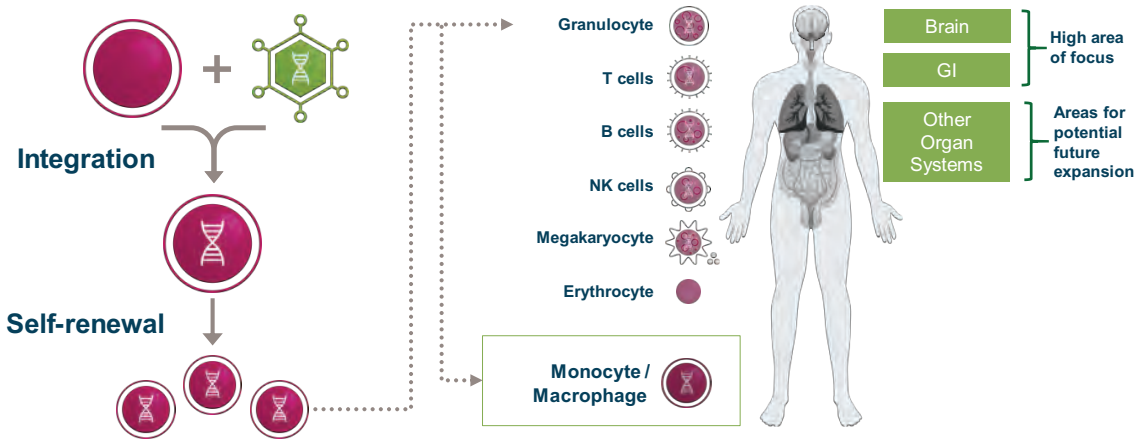
Business Overview (including company strategy, business model, and key performance indicators)

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 product candidates across seven different diseases, with follow-up periods of more than 10 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 three therapeutic disease areas: neurodegenerative, immunological and blood disorders. Our portfolio includes two commercial-stage products approved in Europe, seven lentiviral-based product candidates in clinical-stage development and several other product candidates in preclinical development. Our two lead programs are OTL-200, which was approved in the European Union, or EU, United Kingdom, or UK, Iceland, Liechtenstein and Norway under the brand name Libmeldy for eligible patients with early-onset metachromatic leukodystrophy, or MLD, and OTL-103, which is being investigated for the treatment of Wiskott Aldrich syndrome, or WAS. For each of our lead product candidates, we are in ongoing discussions with regulatory authorities with respect to the clinical and other data required for future regulatory submissions. In late 2020, for instance, the U.S. Food & Drug Administration, or FDA, cleared our investigational new drug, or IND, application for OTL-200, and we plan to complete interactions with the FDA to determine the path to file a biologics license application, or BLA, by mid-2021. We plan to file a marketing authorization application, or MAA, for OTL-103 in Europe by year-end 2021 and a BLA for OTL-103 in the U.S. in 2022.

We have a broad and advanced portfolio of commercial-stage products, 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 cryopreserved formulations of Libmeldy (OTL-200) and OTL-103 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.

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 and expand 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.

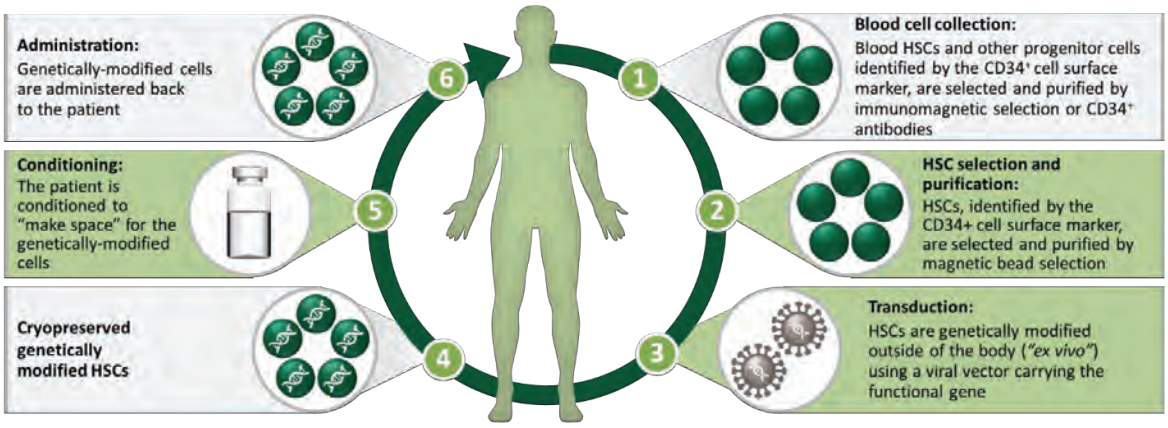
Clinical validation already exists for hematopoietic stem cell transplantation, or HSCT, an approach of treating a patient with a genetic disease with HSCs contributed by a healthy donor individual, thereby using HSCs that contain a functioning copy of the gene of interest. However, this approach has 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 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 plan to market Libmeldy (OTL-200) and 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.

Initially, we are employing our *ex vivo* autologous HSC gene therapy approach in three therapeutic disease areas: neurodegenerative, immunological and blood disorders. 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 initial 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:

- Launch Libmeldy (OTL-200) for the treatment of eligible patients with early-onset MLD in Europe, following its approval in December 2020 and expand geographically into new markets as regulatory approvals are obtained

- Advance our clinical-stage product candidates towards marketing approvals, with a near term focus on OTL-200 for MLD in the U.S., OTL-103 for WAS in Europe and the U.S., and our clinical-stage programs in neurodegenerative disorders, including OTL-203 for MPS-I and OTL-201 for MPS-IIIA

- 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

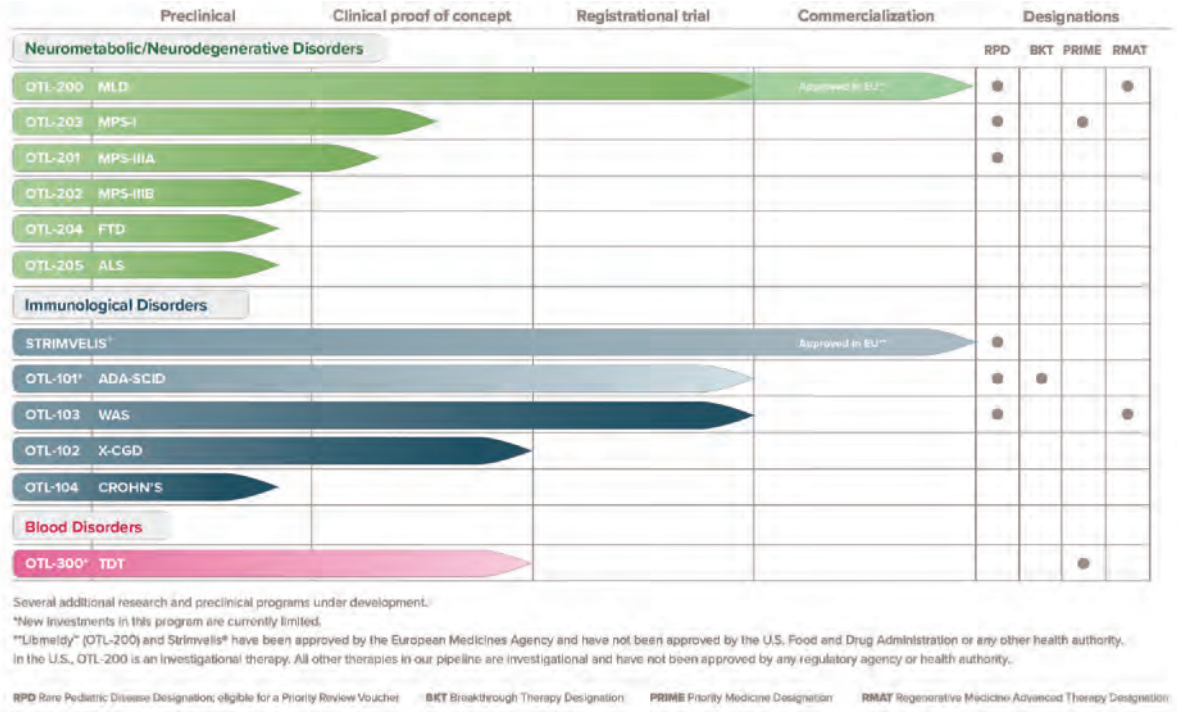
- Establish end-to-end process development, manufacturing and supply chain capabilities, initially through third parties and internally over time
- Establish a patient-centric, global commercial infrastructure, including with third parties in certain regions where we do not have a direct presence
- Execute 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

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. 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 mucopolysaccharidosis type I, or MPS-I, and OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, 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 our commercial program approved in Europe, Strimvelis for adenosine deaminase severe combined immunodeficiency, or ADA-SCID, two advanced registrational clinical programs, OTL-101 for ADA-SCID and OTL-103 for WAS, one clinical proof of concept-stage program, OTL-102 for X-linked chronic granulomatous disease, or X-CGD, and one preclinical program, OTL-104 for Crohn's disease with mutations in the nucleotide-binding oligomerization domain-containing protein 2, or NOD2-CD. Our clinical proof of concept-stage program, OTL-300 for transfusion-dependent beta-thalassemia, or TDT, is focused on a life-threatening blood disorder.

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.

The status of these programs is outlined below:



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, or ARSA, gene 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 GSK, or the GSK Agreement. The clinical trials for this program have been conducted under a GSK-sponsored clinical trial authorization, which was transferred to us during the third quarter of 2018.

Libmeldy approval in Europe as Orphan Drug
In December 2020, the European Commission granted full, or standard, marketing authorization for Libmeldy (OTL-200) (autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced *ex vivo* using a lentiviral vector encoding the human *arylsulfatase-A* (*ARSA*) gene) for the treatment of early-onset MLD characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with i) late infantile or early juvenile forms, without clinical manifestations of the disease, or ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

Libmeldy has received orphan drug designation from the EMA for the treatment of MLD and orphan drug status was maintained at the time of approval. We are continuing to follow patients in the clinical development program for up to 15 years as a post-marketing commitment, and data will be presented to regulators at agreed points in order to further characterize the long-term efficacy and safety of Libmeldy, particularly in the early symptomatic early juvenile population.

Data Supporting the Clinical Profile of Libmeldy
The European Commission 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 2 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 2 years and 3 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≥85 and Gross Motor Function Classification, or GMFC, ≤1). By 4 years post-disease onset, an estimated 62.5% of treated, early-symptomatic EJ MLD patients survived and maintained locomotion and ability to sit without support compared with 26.3% of untreated early-symptomatic EJ MLD patients, representing a delay in disease progression following treatment with Libmeldy.

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

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

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

Ten patients were treated in this trial between April 2017 and April 2020. All patients tolerated the administration well 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.

Data Supporting Safety Profile of Libmeldy
At the time of the integrated data analysis in December 2019, which data set consisted of 29 patients treated with the fresh (investigational) formulation, 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 median duration of follow-up in the first nine patients treated with the cryopreserved (commercial) formulation was 15 months as of March 2020.

The most common adverse reaction attributed to Libmeldy was presence of anti-ARSA antibodies, or AAA. Five out of 35 patients tested positive for AAA at various post-treatment time points. 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. 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.

Additional clinical trial in Europe
A clinical trial in late juvenile patients with MLD is open for recruitment in Milan, Italy.

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. The IND includes a Phase 3b study with inclusion of early symptomatic early juvenile MLD patients and a prospective planned analysis of data from patients already treated in clinical studies in Italy. We plan to complete interactions with the FDA by mid-2021 to determine the path to file a biologics license application, or BLA, with the FDA. In parallel, we plan to initiate a Phase 3b clinical study in the early symptomatic early juvenile MLD patient population, which is planned to commence at a study site in the U.S. in mid-2021 and to be completed as post-BLA commitment.

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 2 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.

Interim results for all eight patients were presented at the WORLD *Symposium* in February 2021. As of November 2020, follow-up in all patients reached at least 12 months and the 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 two 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 the normal range at multiple data points post-treatment. For instance, stable cognitive performance, as evaluated by cognitive age-equivalence using the Bayley scale, was shown in all patients post-treatment, with follow-up ranging from 6 months to 2 years. Longitudinal growth that was within age-appropriate reference ranges was seen in all patients post-treatment, with follow-up ranging from 9 months to 2 years. Furthermore, stable motor function was seen in all patients compared to pre-treatment, with follow-up ranging from 9 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 9 months to 1.5 years.

We have been granted parallel scientific advice by the FDA and EMA on this program. We intend to seek feedback from the regulatory agencies, including on the study design and CMC development, in advance of initiating an international multi-center registrational study for OTL-203 by year-end 2021, subject to filing an IND in the U.S. and necessary clinical trial applications, or CTAs, in Europe.

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

Disease overview

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 one to two years after birth, MPS-IIIA and MPS-IIIB patients begin to experience progressive neurodevelopmental decline, including speech delay and eventual loss of language, behavioral disturbances, and potentially severe dementia. Ultimately, most patients with MPS-IIIA progress to a vegetative state. Life expectancy for patients with MPS-IIIA and MPS-IIIB is between 10 to 25 years and 15 to 30 years, respectively.

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

Limitations of current therapies

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

Our solutions, OTL-201 for treatment of MPS-IIIA and OTL-202 for treatment of MPS-IIIB

We are developing OTL-201 and OTL-202 as *ex vivo* autologous HSC gene therapies for treatment of patients with MPS-IIIA and MPS-IIIB, respectively. In both indications we believe preclinical studies in mice have shown that *ex vivo* autologous gene therapy has the potential to address the neurological manifestations of MPS-IIIA and MPS-IIIB. 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-IIIA and has received rare pediatric disease designation from the FDA.

Proof of concept trial in MPS-IIIA

We are supporting a proof of concept trial for the treatment of MPS-IIIA, which started enrollment in January 2020. The trial, which is being conducted by the Royal Manchester Children's Hospital and sponsored by the Manchester University NHS Foundation Trust, is expected to enroll up to five patients. As of February 2021, four patients were enrolled in the study and three patients had been treated with OTL-201 in the ongoing proof of concept trial.

Interim results were presented at the WORLD *Symposium* in February 2021 through an oral presentation. As of February 2021, these preliminary results from the first three patients treated with OTL-201 showed promising tolerability, engraftment and biomarker data over the initial three-month follow-up period. For instance, the treatment has been generally well-tolerated in the first three patients with no treatment-related SAEs, and all transplant-related SAEs and adverse events have resolved. Data supported evidence of hematological engraftment, as illustrated by the rapid recovery of neutrophils, platelets and hemoglobin levels post myeloablative conditioning in all three patients within three months of treatment. Enrollment is planned to be completed and the company intends to release additional interim results in 2021.

In terms of biomarker data, SGSH enzyme expression in leukocytes and CD15+ cells increased from undetectable levels at baseline to supra-physiological levels at three months in all three patients treated. Furthermore, investigators reported a reduction of urinary GAG levels to within the normal range by three months in the first two patients treated with evaluable data.

Preclinical development of OTL-202
OTL-202 will use the same approach as OTL-201. Lentivirus vector optimization for OTL-202 for treatment of MPS-IIIB is ongoing, and we plan to continue to progress preclinical development of MPS-IIIB. 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
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.

Preclinical studies in a mouse model of FTD are currently under way, and we plan to announce new preclinical data from this research program in the second half of 2021.

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

Gene therapy for treatment of WAS

Disease overview

WAS is a rare, life-threatening inherited disease affecting the patient's immune system and platelets leading to recurrent, severe infections and uncontrollable bleeds, which are the leading causes of death in the disease. WAS is referred to as an "X-linked-recessive" disease as it is associated with a genetic defect on the X chromosome. Because it is an X-linked disease, it affects mainly males. Patients with WAS are born with a defect in the gene that produces the WAS protein, or WASP. As a result, they suffer from life-threatening thrombocytopenia and are at risk of severe bleeds, infections, autoimmunity, malignancies and severe eczema. These symptoms require increasingly frequent hospitalizations. The median survival for a patient with WAS without curative intervention is approximately 15 years. Patients with early onset WAS generally have a shorter life expectancy.

The incidence of WAS is currently estimated at approximately 0.4 in 100,000 live male births.

Limitations of current therapies

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

Our solution, OTL-103 for treatment of WAS

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

We obtained worldwide rights to this program through the GSK Agreement in 2018.

OTL-103 has received orphan drug designation from the FDA and the EMA for the treatment of WAS. OTL-103 has also received a Rare Pediatric Disease Designation from the FDA. RMAT designation was granted in 2019.

Clinical program

Eight patients have been treated with OTL-103 in an ongoing fresh formulation registrational trial at San Raffaele Hospital in Milan, Italy, and nine patients in an expanded access program, or EAP, at the same site, with a follow-up of up to approximately 10 years post-treatment for the first patient treated. In addition, a phase 3, open-label, single arm clinical trial using the intended commercial cryopreserved formulation of OTL-103 was initiated in 2019 and has recruited and treated six patients as of January 2020. All patients have reached a minimum of 12-months follow-up. The co-primary endpoints of the study using the cryopreserved formulation include bleeding (0 to 12 months post-gene therapy) and infections (6 to 18 months post-gene therapy) compared with rates pre-gene therapy.

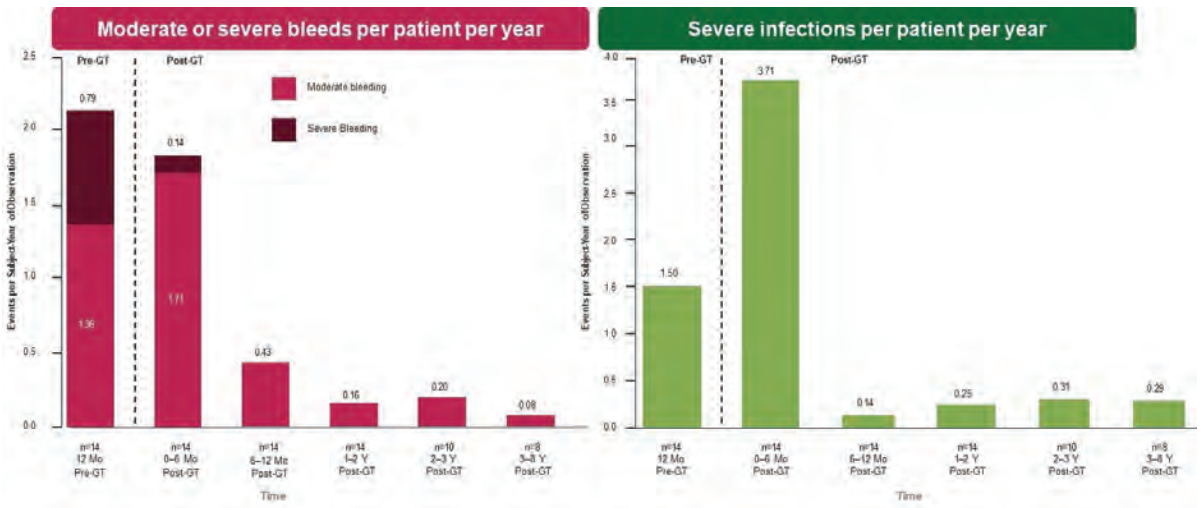
The primary goals of the registrational clinical trial are to assess the efficacy and safety of OTL-103 in WAS patients, as measured by, for example, improved T-cell function, improved platelet count and overall survival at 36 months after treatment. Other goals of this clinical trial include reduced bleeding episodes and reduced frequency of severe infections. The primary analysis for the registrational clinical trial was prospectively defined to be when all patients have completed at least 3 years' follow-up, which was achieved in 2017.

The first interim analysis was generated in 2017, when 6 of the 8 subjects had completed at least 3 years follow up. The results of an interim analysis of this clinical trial were published in 2019 in *Lancet Haematology* and showed that WASP expression in lymphocytes and platelets was substantially improved compared to baseline by six months and remain constant thereafter. At one-year post-treatment with OTL-103, T-cell counts increased in seven evaluable patients, as compared to counts prior to treatment, reaching normal values. Because of the increase in T-cells, a reduction in infections was observed in patient's post-treatment compared to one year prior to treatment with OTL-103.

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

An EAP was put in place after the study completed enrollment. The objective of this EAP was to provide treatment for patients affected by WAS with high unmet medical need in advance of the product being commercially available.

A second interim analysis of patients in the registrational clinical trial and EAP was done in March 2019. As reported at ASH 2019, in patients with at least one year of follow-up in the program (n=14), the absence of severe bleeding events and independence from platelet transfusions were observed in all subjects by 9 months of follow-up. Additionally, a reduction in severe infection rate was observed at multiple time points post-treatment.



Cumulatively, as of January 2021, a total of 23 subjects from clinical trials and an EAP have been treated with OTL-103. Seventeen of the subjects – eight from clinical trials and nine from the EAP – have been treated with the fresh formulation of OTL-103, and six subjects have been treated with the cryopreserved formulation of OTL-103.

From these two trials and the EAP, 18 SAEs were reported in a total of seven subjects during the reporting period. Nine of the 18 events occurred pre-gene therapy in the cryopreserved study of OTL-103. None of these SAEs were considered to be related to OTL-103, no antibodies against WASP were detected, and no allergic reactions related to OTL-103 have been reported in subjects treated with OTL-103. As of December 2020, no new safety information has changed the known safety profile of OTL-103.

Regulatory pathway for OTL-103
An IND for OTL-103 was opened in the U.S. in 2019, and an RMAT multi-disciplinary meeting was held with FDA in 2020. The meeting was intended to discuss the development program completed to date and the path to a BLA filing in the U.S. for OTL-103. Based on feedback received during that meeting, we are currently working to compile the remaining data to support a BLA filing including additional clinical data, CMC comparability data and development of a specific functional potency assay requested by the FDA.

In 2020, we also received scientific advice from EMA to clarify the filing strategy and data required to file an MAA in the EU. We plan to continue engaging with the FDA and EMA in 2021 concerning the manufacturing and clinical development of OTL-103.

We plan to submit an MAA with the EMA and a BLA with the FDA for OTL-103 for the treatment of WAS in 2021 and 2022, respectively.

We currently expect that our MAA and BLA submissions will be supported by a data package, including an adequate potency assay and clinical data from our trial with eight patients treated with the fresh formulation of OTL-103 and data from the second clinical trial using the intended commercial cryopreserved formulation as well as data collected from nine additional patients treated with OTL-103 under an EAP. We intend to seek approval of OTL-103 using mobilized peripheral blood as the cellular source and a cryopreserved product formulation.

Gene therapy for treatment of ADA-SCID
Disease overview
Severe combined immunodeficiency, or SCID, is a rare, life-threatening inherited disease of the immune system. ADA-SCID is a specific form of SCID, commonly known as “bubble-baby disease,” caused by mutations in the ADA gene, resulting in a lack of, or minimal, immune system development, which leaves the patient vulnerable to severe and recurrent bacterial, viral and fungal infections.

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

Patients with ADA-SCID are most commonly diagnosed during the first six months of life based on recurrent bacterial, fungal, and viral infections, persistent lymphopenia, and ADA activity below 1%. Newborn screening for T-cell deficiencies, including ADA-SCID, has now been adopted in all 50 states in the United States, as well as in other jurisdictions, including several Canadian provinces, Israel, Taiwan, Germany, Switzerland, Norway and Sweden.

Limitations of current therapies
The primary treatment options for ADA-SCID are HSCT and enzyme replacement therapy, or ERT. Although HSCT is a potentially curative treatment for ADA-SCID patients, this procedure is associated with a high risk of complications and mortality, with one-year survival rates of 43%, 67% and 86% for transplants from haploidentical donors, human leukocyte antigen, or HLA,-matched unrelated donors and HLA-matched sibling donors, respectively.

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

Our solutions, OTL-101 and Strimvelis for treatment of ADA-SCID
Strimvelis is the only gammaretroviral vector mediated autologous HSC gene therapy in our portfolio. Each of our other pipeline therapies, including OTL-101 for ADA-SCID and OTL-200 for MLD, employ a self-inactivating, or SIN, lentiviral vector-based approach that has been specifically designed to minimize the risk of insertional oncogenesis after administration. No evidence of insertional oncogenesis related to lentiviral vector-based HSC gene therapy has been reported in any of our programs.

Strimvelis
In Europe, our commercial program Strimvelis, an *ex vivo* gammaretrovirus mediated autologous HSC gene therapy, is the only approved gene therapy option for patients with ADA-SCID. The EMA approved Strimvelis in May 2016 for treatment of children with ADA-SCID with no suitable HLA-matched related stem cell donor. Strimvelis consists of HSCs transduced with a gammaretroviral vector encoding the human adenosine deaminase cDNA sequence. Strimvelis is available at a single site in a fresh product formulation at San Raffaele Hospital in Milan, Italy, and has a shelf-life of up to six hours.

Summary of the safety profile of Strimvelis
In October 2020, one case of lymphoid T cell leukemia was reported in a patient approximately five years after such patient was treated with Strimvelis as part of a compassionate use program. We notified the EMA and the relevant local European regulatory authorities of an emerging safety issue and paused treating new patients with Strimvelis pending the completion of the causality investigation. 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, reviewed the updated risk-benefit assessment of Strimvelis as part of its ongoing MAA renewal procedure, concluded that the risk-benefit balance remains favorable and recommended in February 2021 that the marketing authorization for Strimvelis be renewed for five years, allowing marketing of Strimvelis to resume.

As of November 2020, the safety of Strimvelis was evaluated in 40 patients – 22 patients who were treated in the clinical development program, 16 patients treated in the commercial setting, and 2 patients treated with a medicinal product prepared from mobilized peripheral blood under hospital exemption – with a maximum follow-up of 19 years. The reported adverse reactions are in line with the expected safety profile of Strimvelis and the conditioning regime administered prior to treatment

with the product. The most commonly reported adverse reaction was pyrexia. For complete safety details, please see the Summary of Product Characteristics, or SmPC, for Strimvelis, available at the EMA website.

OTL-101 for treatment of ADA-SCID
We are developing OTL-101 as an *ex vivo* autologous lentiviral vector-based HSC gene therapy to treat patients with ADA-SCID through a single administration.

OTL-101 has been investigated in multiple clinical trials in the United States and Europe. As of January 2021, 67 patients have been treated with a drug product manufactured with the EFS-ADA lentiviral vector, with a maximum follow-up of approximately nine years post treatment. Our program comprises a registrational trial conducted at University of California Los Angeles, or UCLA, of 20 patients treated with a fresh product formulation of OTL-101, supportive data derived from a clinical trial of 10 patients treated with a cryopreserved formulation at UCLA and additional data derived from a clinical trial of 10 patients treated with a fresh product formulation at Great Ormond Street Hospital, or GOSH. The remaining 27 patients treated as of January 2021 represent compassionate use patients or patients for whom we do not have adequate follow-up as of the date of this Annual Report but for which safety data is presented in the summary below. Among the 67 patients treated, four patients, including those treated under compassionate use and additional supportive studies, did not engraft or had to resume ERT and/or receive rescue bone marrow transplant.

We obtained worldwide rights to the OTL-101 program through our UCLB/UCLA license agreement and we obtained worldwide rights to the Strimvelis program through our asset purchase and license agreement with Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD, or, together, GSK.

OTL-101 has received orphan drug designation from the FDA and the EMA for the treatment of ADA-SCID and Breakthrough Therapy Designation from the FDA. OTL-101 has also received a Rare Pediatric Disease Designation from the FDA.

Registrational trial conducted by UCLA ("UCLA Fresh study")
Production of the fresh OTL-101 drug product formulation (with bone marrow as the cellular source) used in this clinical trial was performed onsite at UCLA and at the National Institutes of Health, or NIH, for one patient. In this clinical trial, all 20 enrolled and treated patients were treated with ERT prior to enrollment and continued ERT until 30 days following their treatment with OTL-101. Two years follow-up was completed for all patients in August 2018.

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

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

When comparing the overall survival for the OTL-101 treated patients with a historical control group who received allogeneic bone marrow transplant, or HSCT, between 2000 and 2016 (n=26), OTL-101 treated patients achieved a higher overall survival rate at 24 months (100%) versus the group that received allogeneic bone marrow transplant (88%)

Event-free survival is defined as survival without resumption of PEG-ADA ERT or need for rescue allogeneic HSCT. Event-free survival in the OTL-101 treatment group was 100% at 24 months. In comparison, event-free survival in the allogeneic HSCT group was 56%.

Importantly, patients in this trial showed immune cell reconstitution following treatment with OTL-101, which can lead to restoration of both cellular and humoral immune responses. As of the final study report, the severe infection rates across the full post treatment period were lower in the OTL-101 treatment group compared with the HSCT control group. Additionally, by 24 months post-treatment, a considerably higher proportion of subjects in the OTL-101 treatment group (90%) had stopped immunoglobulin replacement therapy compared with HSCT controls (55%).

Supportive clinical trial with UCLA (with cryopreserved formulation) ("UCLA Cryo study")
A cryopreserved formulation of OTL-101 (with bone marrow as cellular source) has been evaluated in a supportive clinical trial at UCLA. Enrollment for this trial is complete and of 10 patients treated, 9 completed their final 24-month study visit as of September 2019. One patient treated in this trial, who did not engraft, restarted ERT, was withdrawn from the trial, and later received a rescue HSCT. The aim of this clinical trial was to provide clinical data supportive of the analytical chemistry, manufacturing, and controls, or CMC, comparison of the fresh and cryopreserved drug product formulations. As of February 2019, when 7 patients had reached 18 months of follow-up, key biological parameters of engraftment and efficacy (including medians of VCN in granulocytes and CD3+ T lymphocyte counts and ADA enzyme activity) were consistent when compared across the UCLA Fresh and UCLA Cryo studies and remained consistent throughout follow-up.

We believe this consistency between the UCLA Fresh and UCLA Cryo studies is supportive of analytical comparability data between the fresh and cryopreserved formulations of OTL-101.

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

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

As of August 2020, overall survival of 100% has been observed at 36 months post treatment in the 10 patients enrolled, and nine patients have achieved event-free survival, with only one patient resuming ERT after 12.2 months due to a failure to engraft. We believe this failure to engraft may, in part, be attributable to the patient's early discontinuation of ERT prior to treatment in contravention of the trial protocol, but may also relate to other clinical factors.

There is a second investigator-sponsored trial being conducted by GOSH, which has now enrolled and treated 10 patients with the cryopreserved product formulation from mobilized peripheral blood. The drug product used in this clinical trial is produced using the same vector and same manufacturing process as the drug product being evaluated at UCLA. Production of the cryopreserved formulation of the drug product used in this clinical trial is performed onsite at GOSH. In this clinical trial, all

patients are being treated with ERT prior to enrollment and continue ERT until 30 days following initial treatment with *ex vivo* autologous HSC gene therapy.

The primary goals of this clinical trial are to assess the safety and efficacy of the investigational drug product in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates. As of January 2021, all ten patients are alive and no longer being treated with ERT.

OTL-101 clinical program safety
As of January 2021, there have been 41 SAEs reported from 16 out of 33 subjects exposed to OTL-101 in the EAP and UCLA Fresh and UCLA Cryo studies. Based on the safety data collected in the OTL-101 clinical development, expanded access and compassionate use programs, OTL-101 has so far demonstrated a favorable safety profile.

A global observational long-term follow-up study is now open. This study is designed to collect long team safety and efficacy data from ADA-SCID patients previously treated with autologous *ex vivo* gene therapy products based on the EFS-ADA lentiviral vector up to 15 years post gene therapy in compliance with current regulatory requirements.

We have completed final clinical study reports for our registrational trial using OTL-101 fresh formulation and the second clinical trial using OTL-101 cryopreserved formulation, which we believe supports the analytical comparability data between fresh and cryopreserved drug product formulations.

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

The incidence of X-CGD is currently estimated to be one in 200,000 male live births.

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

Our solution, OTL-102 for treatment of X-CGD
We are developing OTL-102 as an *ex vivo* autologous HSC gene therapy to treat patients with X-CGD through a single administration. OTL-102 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood or bone marrow, then modified to add a functional *CYBB* gene using a

lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen.

We obtained worldwide rights to the OTL-102 program through an option and license agreement with Généthon, pursuant to which we have exercised an option to certain intellectual property and clinical data associated with clinical trials at sites in the United States and the United Kingdom.

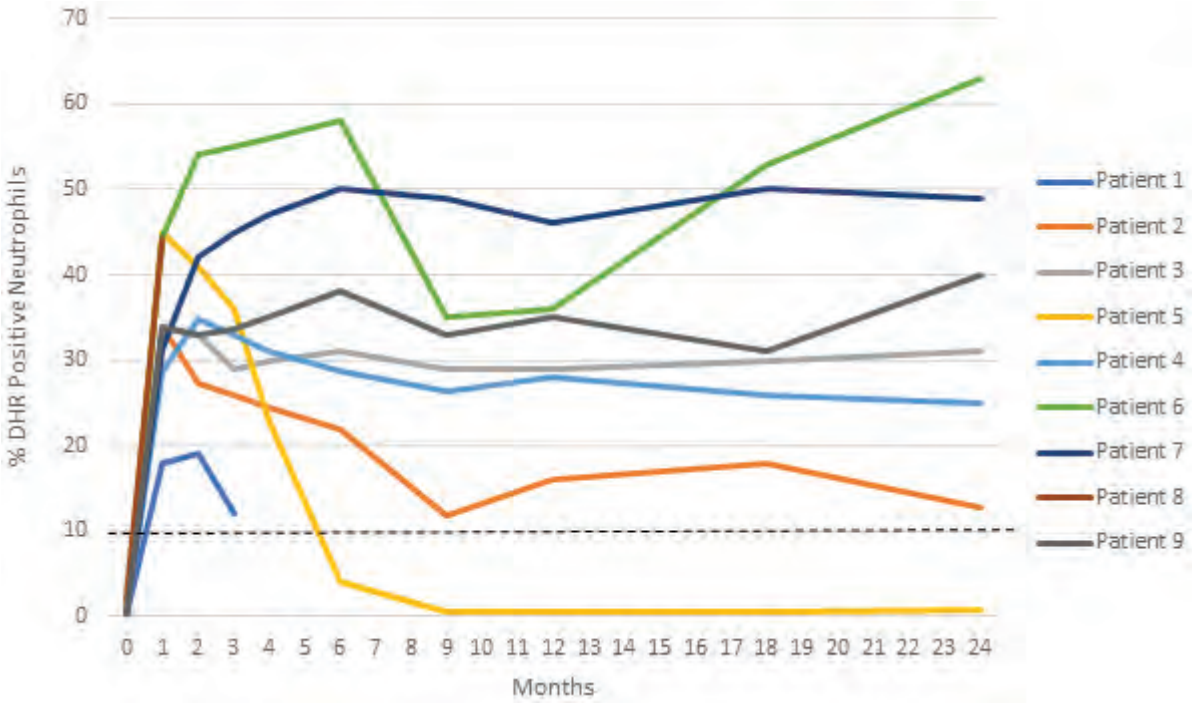
OTL-102 has received orphan drug designation from the EMA and FDA for the treatment of X-CGD.

Ongoing clinical trials
OTL-102, which has been studied in two investigator-sponsored proof of concept clinical trials in the United States and in Europe, with target enrollment of 10 patients in a clinical trial sponsored by UCLA in the United States and an initial target enrollment of five patients in a clinical trial conducted by GOSH in Europe. The clinical trial sites included Boston Children's Hospital, the NIH, and UCLA in the United States, and GOSH and The Royal Free Hospital in London. Patients enrolled in these trials have advanced and severe stages of X-CGD. Manufacture of the drug product occurred at each of these sites using the same vector. As of January 2021, nine patients had been treated in the clinical trial in the United States, five of which were treated with a fresh product formulation and four of which were treated with a cryopreserved formulation. Further, three patients had been treated in the clinical trial in Europe, and one patient was treated in a compassionate use program in Europe with a cryopreserved product formulation. In the future, we may treat additional pediatric patients in this trial with a cryopreserved formulation of OTL-102.

OTL-102 has shown sustained *CYBB* expression for over two years in six patients to date, with a follow-up of three years post-treatment in patients as of January 2021.

In these clinical trials, the production of NADPH-oxidase activity in neutrophils, a biomarker that demonstrates restored granulocyte function, has been measured in patients for up to 24 months post-treatment. In a November 2019 publication in *Nature Medicine*, combined data from nine patients, including initial enrollees in both clinical trials and a compassionate use patient, showed NADPH-oxidase activity, as measured by dihydrorhodamine, or DHR, assay, above 10% in six patients with at least 24 months follow-up. Based on the scientific literature, levels of NADPH-oxidase activity above 10% was a clinically meaningful percentage for fighting infections successfully. One pediatric patient showed initial engraftment of DHR+ cells followed by a decrease to levels of 1% or less. The graphic below illustrates sustained NADPH-oxidase levels, as measured for up to 24 months post-treatment.

OTL-102 (X-CGD): NADPH-oxidase activity(1)



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

Since September 2018, four additional patients have been treated as part of the clinical trials, with one adult patient having sustained DHR+ neutrophils of 77.2% at 6 months and three pediatric patients displaying a similar response to the pediatric patient that did not respond to therapy. These observations specific to the pediatric patients were investigated and amendments to the clinical protocols were made in 2020 to modify the conditioning regimen used in studies with the aim of improving engraftment. Factors that are considered important to address are the chronic inflammatory environment of the bone marrow in CGD patients, the potential for B and T cell immune responses, either as a result of the disease background or as newly generated due to the 'novel' expression of gp91phox and the quality of the drug product which may be influenced by the quality of the collected cells. Investigators plan to begin enrolling additional pediatric patients (n=6) in 2021 and 2022 to access outcomes in the specific patient's population. The primary goals of this extension clinical trial are to assess safety and efficacy, as measured by biochemical and functional reconstitution through increased nicotinamide adenine dinucleotide phosphate-oxidase, or NADPH oxidase, activity in progeny of engrafted cells and stability at 12 months post-treatment. Following institutional review board, or IRB, approvals, enrollment can commence. We intend to follow these pediatric patients in the proof of concept study and then progress OTL-102 into a registrational study.

Two patients treated with OTL-102 as part of the clinical trials died during the three months period following treatment as a result of pre-existing disease-related complications present at the time of treatment with OTL-102. One of these patients (from the UK trial) died of acute respiratory distress syndrome. This subject had a pre-existing lung condition. The other patient (from the U.S. trial) developed platelet antibodies due to sensitization after several granulocyte infusions the patient received prior to gene therapy. The learnings from this patient resulted in a protocol amendment to

prevent patients with existing platelet antibodies from enrolling in the trial. Neither of these two fatalities was deemed by the investigator to be related to the therapy. A third fatality was reported involving a patient treated under the compassionate use program at GOSH. Because of this patient's advanced disease stage at the time of enrollment, the patient required a surgical procedure following treatment and died as a result of complications from this procedure. This fatality was deemed by the investigator not to be related to the product.

Safety
As of March 2020, the date of the most recent safety data available to us, patients treated in this clinical trial indicate OTL-102 was generally well-tolerated. There were 26 serious adverse events reported, one of which was assessed by the investigator as being possibly related to OTL-102 and was reported as Immune Reconstitution Inflammatory Syndrome (IRIS). As of December 2020, no new safety information received by us has changed the known safety profile of OTL-102.

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 completed to date has shown that NOD2 defective human and NOD2 deficient murine macrophages and monocytes are refractory to bacterial MDP stimulation. We have demonstrated the successful restoration of NOD2 expression and functional correction of macrophage cellular responses to bacterial MDP stimulation, in NOD2 defective human cells and NOD2 deficient murine cells, achieved through lentiviral gene transfer of NOD2 to human $CD34^+$ HSC and murine lineage negative cells, respectively.

We plan to continue to progress our preclinical proof of concept studies using an experimental mouse model of NOD2 deficiency to evaluate the use of gene modified HSC-derived cells to replace intestinal gut resident macrophages (monocyte-derived) and to correct inflammation and colitis associated with NOD2-CD. We plan to announce new preclinical data from this research program in the second half of 2021.

Blood disorders

Gene therapy for treatment of TDT

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

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

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

Our solution, OTL-300 for treatment of TDT
OTL-300 is an *ex vivo* autologous HSC gene therapy, manufactured from HSCs isolated from the patient's own mobilized peripheral blood, then modified to add a functional HBB gene using a lentiviral vector. OTL-300 is designed to significantly reduce or eliminate the need for blood transfusions in patients with TDT.

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

In May 2020, we announced that we would be reducing our investment in the future development of OTL-300.

Proof of concept trial (cryopreserved formulation)
OTL-300 has been investigated in an academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The study and clinical follow-up completed in November 2019. Nine patients with severe TDT received a single intra-osseous infusion of a cryopreserved formulation of OTL-300 and were followed up for 2 years. The patients evaluated in this trial included six pediatric patients aged three to 17 years, and three adult patients aged 18 years and over. On completion of the study, all patients enrolled in an Orchard-sponsored long-term follow-up clinical trial, which will continue assessments for an additional six-year period.

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

All patients have completed the 24-month study follow-up period. Transfusion independence or significant reductions in transfusion frequency and volume requirements were observed in six patients, with four of the six pediatric patients being transfusion-free since approximately one-month post-treatment. Following treatment, substantial reductions (in excess of 50%) in transfusion volume requirements were observed over a period of at least 3 years in two out of three adult patients, one of whom had a 9-month transfusion-free period during the first-year post-treatment.

As of July 2020, OTL-300 was generally well-tolerated. Six SAEs were reported in four subjects out of nine patients treated, and each such SAE was assessed as not related to treatment with OTL-300. None of these SAEs were fatal, and all events resolved. As of December 2020, no new safety information received has changed the safety profile of OTL-300.

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 initial 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. In 2020, we introduced new programs in larger indications and 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, OTL-103 for WAS, 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 our 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, OTL-103, and OTL-101 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-300, 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

Following our receipt of full, or standard, marketing approval from the European Commission for Libmeldy (OTL-200) for the treatment of early-onset MLD, we expect to launch Libmeldy in Europe and generate product sales as early as the first half of 2021. In preparation for a European launch, we have substantially completed our build-out of our commercial operations in Europe with a 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 the use of 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 adding employees with broad experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement. We expect to continue expansion of these capabilities throughout 2021 and beyond 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, sequentially 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. For European markets, we anticipate the list price of Libmeldy to be in the range of €2.5 to €3 million for a one-time treatment, which is 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 for each of our products/product candidates, patents, know-how and trade secrets associated with each of our products/product candidates. However, we do not own any patents or patent applications that cover Libmeldy, Strimvelis or any of our lead product candidates. We in-license from UCLB and UCLA one family of patents directed at OTL-101, which are issued in the U.S. and Europe We cannot guarantee that patents will issue from any of existing patent applications or from any patent applications we or

our licensors may file in the future, nor can we guarantee that any patents that may issue in the future from such patent applications will be commercially useful in protecting our products/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. However, know-how and trade secrets can be difficult to protect. Although we take steps to protect our know-how, trade secrets and other proprietary information, including restricting access to our premises and our confidential information, as well as entering into agreements with our employees, consultants, advisors and potential collaborators, third parties may independently develop the same or similar know-how, trade secrets or proprietary information or may otherwise gain access to such know-how, trade secrets and other proprietary information or such know-how, trade secrets or other proprietary information may otherwise become known. Moreover, we cannot guarantee that our confidentiality agreements will provide meaningful protection or that they may not be breached and we may not have an adequate remedy for any such breach. As a result, we may be unable to meaningfully protect our know-how, trade secrets and other proprietary information.

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

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

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

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

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

License agreements

GSK asset purchase and license agreement

In April 2018, we entered into the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for 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 are required to first use best endeavors to file an MAA for OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. In December 2020, we received full, or standard, marketing authorization for Libmeldy in the European Union as well as the United Kingdom, Iceland, Liechtenstein and Norway. We are also required to use best endeavors to file a BLA for OTL-103 for WAS in the United States and to use commercially reasonable efforts to file an MAA for OTL-103 in Europe, and to subsequently market, sell and promote OTL-103 in such jurisdictions. We are also required to use commercially reasonable efforts to develop and file an MAA or BLA, as applicable, for OTL-300 for TDT in either the United States or Europe. In addition, we must also use best endeavors to maintain the MAA and regulatory designations for Strimvelis in the European Union and to continue to make Strimvelis available to eligible patients until an alternative gene therapy product has received marketing approval in Europe. We must also continue to make Strimvelis available at the San Raffaele Hospital for as long as a minimum number of patients are treated and entitled to receive reimbursement for the provision of Strimvelis, over a defined period. We intend to continue to make Strimvelis available for so long as we are required to do so under the GSK Agreement.

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

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. We will pay a mid-single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the 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 and/or commercialization activities of any of the programs under the GSK Agreement, upon the occurrence of an SAE, or if we believe such program poses a safety risk to patients. GSK may require us to grant a third party a non-exclusive license under the intellectual property we have acquired from GSK under the GSK Agreement if we materially breach of our obligations to use best endeavors and/or commercially reasonable efforts to develop and commercialize the acquired programs and fail to develop and implement a mutually agreeable plan to cure such material breach within a specified time period. The foregoing license only continues until such time as we cure our material breach and we must pay GSK all amounts we receive from the third party in connection with such license.

Telethon-OSR research and development collaboration and license agreement

In April 2018, in connection with our entering into the GSK Agreement, we entered into a deed of novation with GSK, Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, pursuant to which we acquired and assumed all of GSK's rights and obligations under the R&D Agreement with Telethon-OSR for the research, development and commercialization of *ex vivo* HSC gene therapies for ADA-SCID, WAS, MLD, 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, TDT. At the time we entered into the deed of 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 to the deed of novation.

Under the R&D Agreement, Telethon-OSR is required to use commercially reasonable efforts to conduct each of the collaboration programs in accordance with development plans approved by a joint steering committee. With respect to those programs in relation to which our option has been exercised, we are required to use commercially reasonable efforts to develop, obtain regulatory approval, launch and promote in both the European Union and the United States all licensed products

and to commercialize and manufacture such products at levels sufficient to meet commercial demands. We are required to use best efforts to renew the European Union marketing authorization for Strimvelis to enable patients to be treated at the San Raffaele hospital from all referring centers globally, as permitted by applicable law. We are responsible for the costs and activities associated with the continued development of Strimvelis and each program for which an option under the R&D Agreement is exercised.

As consideration for the licenses and options granted under the R&D Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are obligated to pay up to an aggregate of €31.0 million in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (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.

UCLB/UCLA license agreement

In February 2016, we entered into a license agreement, or the UCLB/UCLA Agreement, with UCLB and UCLA, pursuant to which we obtained an exclusive, worldwide, sublicensable license to certain technology, clinical data, manufacturing know-how, and intellectual property rights related to the production of virally transduced HSCs for treatment of patients with ADA-SCID, in addition to certain other rare disease indications. We must use diligent efforts to develop and commercialize a gene therapy product in each of the foregoing indications in the United States, United Kingdom and at least one of France, Germany, Italy and Spain as soon as reasonably possible.

Under the UCLB/UCLA Agreement, we are also obligated to pay UCL royalties ranging from low to mid-single-digit percentages on net sales of each of the product candidates subject to the UCLB/UCLA Agreement that receive marketing approval. Our royalty obligations under the UCLB/UCLA Agreement terminate in February 2041. In addition, we are required to pay to UCLB milestone payments up to an aggregate of £28.9 million ($37.9 million as of December 31, 2019)

upon achievement of our first, second and third marketing approvals of product candidates under the UCLB/UCLA Agreement.

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

Oxford BioMedica license and development agreement

In November 2016, we entered into a license and development agreement, or the Oxford Development Agreement, with Oxford BioMedica (UK) Limited, or Oxford BioMedica, for the development of gene therapies for ADA-SCID, MPS-IIIA and certain other diseases that we may request be included under the Oxford Development Agreement, such other diseases referred to as Subsequent Indications. The Oxford Development Agreement was amended on multiple occasions and most recently in April 2020.

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

As consideration for the licenses granted under the agreement, we issued 588,220 of our ordinary shares to Oxford BioMedica. We are also obligated to issue additional equity upon the achievement of certain milestones, pursuant to which we issued 150,826 ordinary shares upon the achievement of the first milestone in November 2017 and 150,826 ordinary shares were issued upon the achievement of further milestones in August 2018. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica. Additionally, we are obligated to pay low single-digit 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, and Passage Bio also has a preclinical development program for MLD. 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.
- **MPS-IIIA**: There are currently no effective disease modifying treatment options for patients with MPS-IIIA. We are aware of three gene therapy candidates in clinical development. In collaboration with Sarepta Therapeutics, Lysogene is developing an AAV gene therapy product administered through intracerebral injections; 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-IIIA. Currently we are not aware of any companies developing ERTs for MPS-IIIA.

- **WAS**: The current standard of care for WAS is HSCT. Patients who are unable to match with a blood donor or who are otherwise ineligible for HSCT may pursue palliative care options, including intravenous immunoglobulin and antimicrobials to prevent and treat infections, topical corticosteroids to manage outbreaks of eczema, platelet transfusions to treat severe bleeds, and immunosuppressive drugs, such as rituximab (Rituxan), to counter autoimmune manifestations. Splenectomy may also be used to treat thrombocytopenia. These palliative approaches do not slow disease progression or address the underlying cause of WAS. In June 2020, CSL Behring and Seattle Children's Research Institute announced an early-stage research collaboration to develop a *ex vivo* HSC gene therapy for WAS. We are also aware that Généthon and Boston Children's Hospital are sponsoring clinical trials with *ex vivo* HSC gene therapy.
- **X-CGD**: Disease management options for patients with X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma therapy. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. We are not aware of any other competing clinical or preclinical programs in X-CGD.
- **ADA-SCID**: The current standards of care for the treatment of ADA-SCID are HSCT and chronic ERT. In October 2018, the FDA approved elapegademase-lvlr (Revcovi), a PEGylated recombinant ADA ERT marketed by Leadiant Biosciences to treat ADA-SCID.
- **TDT**: The current standard of care for the treatment of TDT involves chronic blood transfusions to address anemia combined with iron chelation therapy to manage the iron overload often associated with such chronic blood transfusions. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. TDT is a highly competitive research area in gene therapy, with one *ex vivo* HSC gene therapy treatment already approved in Europe (Zynteglo) and several novel approaches under investigation, notably gene editing. Other non-gene therapy approaches have been approved *(e.g.*, Reblozyl) or are under investigation to improve treatment outcomes in broader populations of beta-thalassemia. Other programs for TDT include a clinical stage *ex vivo* gene editing program from Vertex Pharmaceuticals and CRISPR Therapeutics, and a preclinical *ex vivo* gene editing program from Editas Medicine.
- **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.
- **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 had historically been subject to review by the Recombinant DNA Advisory Committee, or RAC, of the NIH, Office of Biotechnology Activities, or the OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. While the NIH Guidelines are not mandatory unless the research in question 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. On August 17, 2018, the NIH issued a notice in the Federal Register and issued a public statement proposing changes to the oversight framework for gene therapy trials, including changes to the applicable NIH Guidelines to modify the roles and responsibilities of the RAC with respect to human clinical trials of gene therapy products, and requesting public comment on its proposed modifications. During the public comment period, which closed October 16, 2018, the NIH announced that it will no longer accept new human gene transfer protocols for review as a part of the protocol registration process or convene the RAC to review individual clinical protocols. In April 2019, NIH announced the updated guidelines, which reflect these proposed changes, and clarified that these trials will remain subject to the FDA's oversight and other clinical trial regulations, and oversight at the local level will continue as set forth in the NIH Guidelines. 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. Further, NIH renamed the RAC the Novel and Exceptional Technology and Research Advisory Committee, or NExTRAC, and revised its role to provide recommendations to the NIH Director and a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies.

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 COVID-19 pandemic, restrictions preventing the conduct or completion of facility or clinical site inspections can 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 of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making in the United States a drug or biological product for such disease or condition will be received from sales in the United States of such drug or biological product. The sponsor of a product candidate for a rare pediatric disease may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug or biological product application after the date of approval of the rare pediatric disease drug or biological product, referred to as a priority review voucher, or PRV. A sponsor may request rare pediatric disease designation from the FDA prior to the

submission of its BLA. A rare pediatric disease designation does not guarantee that a sponsor will receive a PRV upon approval of its BLA. Moreover, a sponsor who chooses not to submit a rare pediatric disease designation request may nonetheless receive a PRV upon approval of their marketing application if they request such a voucher in their original marketing application and meet all of the eligibility criteria. If a PRV is received, it may be sold or transferred an unlimited number of times. Congress has extended the PRV program through September 30, 2024, with the potential for PRVs to be granted through September 30, 2026.

Expedited development and review programs

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

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

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

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

RMAT designation

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

Post-approval requirements

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

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"),

industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

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

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The 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.

European Union 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 the European Union, for example, a CTA must be submitted for each clinical trial to each country's National Competent Authority, or NCA, and at least one independent Ethics Committee, or EC, much like the FDA and an IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical trial may proceed. Under the current regime (the EU Clinical Trials Directive 2001/20/EC and corresponding national laws) all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred.

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. It will overhaul the current system of approvals for clinical trials in the European Union. Specifically, the new regulation, which will be directly applicable in all Member States (meaning that no national implementing legislation in each European Union Member State is required), aims at simplifying and streamlining the approval of clinical trials in the European Union. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single entry point and strictly defined deadlines for the assessment of clinical trial applications. It is expected that the new Clinical Trials Regulation (EU) No 536/2014 will come into effect following confirmation of full functionality of the Clinical Trials Information System, the centralized European Union portal and database for clinical trials foreseen by the new Clinical Trials regulation, through an independent audit, which is currently expected to occur in December 2021.

Drug review and approval in the EEA

In the European Economic Area (comprised of the European Union Member States plus Norway, Iceland and Liechtenstein), or EEA, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the EEA 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 EEA, and we anticipate that our gene therapy development products would also be regulated as ATMPs in the EEA.

To obtain regulatory approval of an ATMP under EEA 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 European Union, with the exception of, among other things, certain specific requirements set out in 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 EEA. As provided for in the ATMP Regulation, the scientific evaluation of MAAs for ATMPs is primarily performed by a specialized scientific committee called the Committee for Advanced Therapies, or CAT. The CAT prepares a draft opinion on the quality, safety and efficacy of the ATMP which is the subject of the MAA, which is sent for final approval to the Committee for Medicinal Products for Human Use, or CHMP. The CHMP recommendation is then sent to the European Commission, which adopts a decision binding in all EEA Member States. The maximum timeframe for the evaluation of a 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 of the CAT and/or CHMP. Clock stops may extend the timeframe of evaluation of a 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 interest from the point of view of public health and, in particular, 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 Irish 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 drug designation and exclusivity

Products with an orphan designation in the EEA 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 EEA 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 EEA 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 the prevalence of such condition must not be more than five in 10,000 persons in the EEA when the application is made, or without the benefits derived from orphan status, it must be unlikely that the marketing of the medicine would generate sufficient return in the EEA 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 EEA, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Otherwise, orphan medicine marketing exclusivity may be revoked only in very select cases, such as if:

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

Pediatric development
In the EEA, 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 marketing authorization application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted 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 marketing authorization application will be made through the centralized procedure. Eligible products must target conditions for which where 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 marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the CHMP or CAT are appointed early in 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 United Kingdom
In June 2016, the electorate in the United Kingdom voted in favor of leaving the European Union (commonly referred to as "Brexit"). Thereafter, in March 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The United Kingdom formally left the European Union on January 31, 2020. A transition period began on February 1, 2020, during which European Union pharmaceutical law remained applicable to the United Kingdom. This transition period ended on December 31, 2020. Since the regulatory framework in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union Directives and Regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom as United Kingdom legislation now has the potential to diverge from European Union legislation. It remains to be seen how Brexit will impact regulatory requirements for product candidates and products in the United Kingdom in the long-term. The MHRA, the United Kingdom medicines and medical devices regulator, has recently published detailed guidance for industry and organizations to follow from January 1, 2021 now that the transition period is over, which will be updated as the United Kingdom's regulatory position on medicinal products evolves over time. Brexit has also created uncertainty with regard to data protection regulation in the United Kingdom, and in particular, how data transfers from the European Union to the United Kingdom will be regulated. The European Union and the United Kingdom have agreed a bridging period of up to 6 months to allow the continued free flow of data from the European Union to the United Kingdom, during which time the European Commission will assess whether the United Kingdom will be granted adequacy status. There is no certainty that an adequacy decision will be granted. If it is not, legal uncertainties regarding the flow of data across borders could increase the complexity and cost of transferring personal data from the European Union to the United Kingdom.

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 will 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.

In addition to the above, on November 20, 2020, the Office of Inspector General, or OIG, finalized further modifications to the federal Anti-Kickback Statute. Under the final rules, OIG added safe harbor protections under the Anti-Kickback Statute for certain coordinated care and value-based arrangements among clinicians, providers, and others. The final rule (with some exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, these rules will have on our business.

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 (GDPR), which became effective on May 25, 2018. 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, 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, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 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. In addition, the GDPR includes restrictions on cross-border data transfers. 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.

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 January 2017, President Trump has signed two executive orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the ACA. On January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. The Trump administration has 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. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. 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 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.

Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a federal district court in Texas ruled the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional, and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case and held oral arguments on November 10, 2020. It is unclear what effect this will have on the status of the ACA and our business. 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 Affordable Care Act risk adjustment program in response to the outcome of the 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, starting in 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 January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA -mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices; however, on December 20, 2019, 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. Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. The Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole".

Other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction of at least $1.2 trillion for fiscal years 2012 through 2021, triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect beginning on April 1, 2013 and, due to legislation amendments to the statute, including the BBA, will stay in effect through 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, 2021 due to the COVID-19 pandemic. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 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. 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 and has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

Further, on July 24, 2020 and September 13, 2020, President Trump signed several Executive Orders aimed at lowering drug pricing that seek to implement several of the administration's proposals. The FDA also released a final rule 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. 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 will be 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 will apply in all U.S. states and territories for a seven-year period beginning January 1, 2021 and ending December 31, 2027. The Interim Final Rule has not been finalized and is subject to revision and challenge. Additionally, on November 20, 2020, HHS finalized 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. 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, Congress has indicated that it 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.

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

Coverage and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any gene therapies for which we obtain regulatory approval. In the United States and markets in other countries, sales of any gene therapies for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and reimbursement from payors. Payors include government authorities, managed care providers, private health insurers and other organizations. 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.

Key Performance Indicators (KPIs)

We do not consider traditional financial measures to be key performance indicators at this stage of development of our business. Management closely monitors cash position and runway, as well as our research and development expenses. In addition, we assess our performance through clinical and regulatory advancement of our programs. In 2020, we unveiled a new Company strategic plan prioritizing our high need and high value indications, as well as expansion into less rare indications. From a clinical perspective, we began research on and announced new preclinical programs in frontotemporal dementia with progranulin mutations (GRN-FTD), amyotrophic lateral sclerosis (ALS), and the NOD2 mutation as a Crohn's disease genetic target. Additionally, we have presented interim data from ongoing proof-of-concept trial for OTL-203 for MPS-I. From a regulatory perspective, In December 2020, our lead program OTL-200 was approved in the EU, United Kingdom, Iceland, Liechtenstein and Norway under the brand name Libmeldy for eligible patients with early onset MLD. Further, in November 2020, we announced FDA clearance for an IND application for OTL-200 in the United States.

Employees and Human Capital Resources

As of December 31, 2020, and 2019 we had 224 and 253 full-time employees, respectively. 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 are 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. In 2020, we launched a comprehensive initiative to enhance diversity, inclusion and belonging.

Summary of the Principal Risks and Uncertainties

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, OTL-103 for Wiskott Aldrich syndrome, or WAS, 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 FDA, and/or the European Medicines Agency, or EMA, 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 not be successful in commercializing Libmeldy or our product candidates if and when approved, and 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, Strimvelis 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 product candidates.
- 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.
- 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 adverse effect on our business.
- We have in the past, and in the future may, enter into collaborations with third parties to develop or commercialize product candidates. If these collaborations are not successful, our business could be adversely affected.
- The market price of our ADSs may be highly volatile and may fluctuate due to factors beyond our control.

Information on Environmental Matters

The Company is required to measure and report its greenhouse gas emissions in accordance with the provisions of the UK Companies Act 2006 (UK Statutory Strategic Report and UK Statutory

Directors' Report) Regulations 2013. Our greenhouse gas emissions estimates for 2020 has been prepared in accordance with the U.K. Government's Department for Environment, Food and Rural Affairs (Defra) guidance document "Environmental Reporting Guidelines: Including Mandatory GHG emissions reporting guidance, from March 2019".

	2020	2019
Estimated greenhouse gas emissions from purchased electricity, heat, steam, or cooling for our own use (tCO^2e)	230.5	303.6
Intensity ratio: Total greenhouse gas emissions per employee on the basis of a monthly average of 250 full-time equivalent employees (2019: 212)	0.9	1.4

We have used evidence and estimates derived from evidence provided by our energy supply partners and lessors to generate our disclosure of emissions for the year. These include the purchase of electricity, heat, steam or cooling either directly from our energy supply partners, or through utility bills from our lessors. Standard emission factors from Defra's GHG Conversion Factors Repository were applied to estimate emissions. The Group considers that the intensity ratio of tonnes of carbon dioxide per full-time equivalent employee is a suitable metric for its operations.

Electricity, heating, and cooling usage at our leased facilities in the United States and United Kingdom drive the majority of our greenhouse gas emissions. Greenhouse gas emissions generated by company-owned facilities declined in 2020 as compared to 2019 as we transitioned to a remote workforce due to the COVID-19 pandemic.

Diversity

Appointments within the Group are made on merit according to the balance of skills and experience offered by prospective candidates. While acknowledging the benefits of diversity, individual appointments are made irrespective of personal characteristics such as race, disability, gender, sexual orientation, religion, or age. A breakdown of employment statistics as of 31 December 2020 and 2019 is as follows:

31 December 2020:

	Male	Female	Total
Company Directors	7	2	9
Executives/Vice Presidents	17	12	29
Other Employees	72	124	196
Total Employees	89	136	225

31 December 2019:

	Male	Female	Total
Company Directors	7	2	9
Executives/Vice Presidents	20	9	29
Other Employees	97	127	224
Total Employees	117	136	253

Section 172(1) UK Companies Act 2006

The Directors are required by law to act in good faith to promote the success of the Company for the benefit of the shareholders as a whole and are also required to have regard for the following areas:

The board has had regard to the following matters:	More information
-the likely consequences of any decision in the long-term;	Refer to the "Business Overview" section of this Strategic Report (page 21) The Group will need substantial additional funding to support continuing operations and pursue a growth strategy as outlined in our Business overview within this Strategic Report. Until such time the Group can generate significant revenue from product sales, if ever, the Group expects to finance operations through a combination of equity offerings, debt financings, collaborations, government contracts or other strategic transactions. The Group may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favourable terms, or at all.
-the interests of the Company's employees;	Refer to the "Employees and Human Capital Resources" (page 82) and "Diversity" (page 84) sections of this Strategic Report The Board and Company management have a good relationship with the Group's employees. The Board maintains constructive dialogue with employees through the Company's Executive Leadership. Appropriate remuneration and incentive schemes are maintained to align employees' objectives with those of the Group.
-the importance of developing the Company's business relationships with suppliers, customers and others;	Refer to the "Summary of the Principal Risks and Uncertainties" section of this Strategic Report (page 82)
-the impact of the Company's operations on the community and the environment;	Refer to the "Employees and Human Capital Resources" (page 82), "Diversity" (page 84), and "Information on Environmental Matters" (page 83) sections of this Strategic Report
-the desirability of the Company maintaining a reputation for high standards of business conduct;	The Board sets high standards for the Company's employees, officers and directors. Implicit in this philosophy is the importance of sound corporate governance. The Group has established a Code of Business Conduct and Ethics (the "Code"), which is posted in the Corporate Governance section of the Group's website and includes mechanisms for reporting suspected violations of the Code and other policies and procedures of the Company. The Company's employees, officers and directors must review the Code periodically and are required to comply with its terms.

The board has had regard to the following matters:	More information
-The need to act fairly as between shareholders of the Company	The Board endeavors to maintain good relationships with its shareholders and treat them equally. The Board values good relations with the Company's shareholders and understands the importance of effectively communicating the Company's operational and financial performance as well as its future strategy. The Company's website provides financial information as well as historical news releases and matters relating to corporate governance. Annual and interim results are communicated via press releases, and are filed with the U.S. Securities and Exchange Commission, as are certain operational and regulatory press releases. Shareholders may also attend the Annual General Meeting where they can discuss matters with the Board.

This report was approved by the board of directors on 9 April 2021 and signed on behalf of the board of directors by:

Bobby Gaspar
Director
9 April 2021

UK STATUTORY DIRECTORS' REPORT

The directors of Orchard Therapeutics plc (the "Company", "Parent Company", or the "Group") submit this report and the audited consolidated financial statements as of and for the year ended 31 December 2020. The information in this report, including the information that is referred to below, shall be deemed to comply with the UK Companies Act 2006 requirements for the UK Statutory Directors' Report. Some disclosures which would typically be included in the UK Statutory Directors' Report have instead been included in the UK Statutory Strategic Report.

General Information

Description of the principal activities and likely future developments of the group's business
The principal activities and likely future developments of the group are outlined in the Strategic Report, beginning on page 20 of this annual report.

Indication of the likely future developments of the group's business

Research and development activities
A fulsome view of the Company's research and development activities is outlined for the Company's key programs in the Strategic Report. Total consolidated research and development expense during the year was $93.7 million (2019: $117.4 million).

Results and dividends
The Company's consolidated financial results for the year are set out on page 131 of this annual report. For the year ended 2020 the directors do not recommend the payment of a dividend (2019: nil).

Directors
The directors of the Parent Company who held office during the year and up to the date of signing of the consolidated financial statements, unless otherwise stated, are outlined in the "Company Information" section on page 2 of this Annual Report.

Capital Structure
Details of the issued share capital, together with details of shares issued during the year, are set out in note 12 to the consolidated financial statements. Share capital activity for the 2020 fiscal year is outlined on page F-3 of the consolidated financial statements in the Consolidated Statement of Shareholders' Equity.

Political Contributions
No political donations were made, and no political expenditure was incurred, by the Company, during 2020 (2019: nil).

Post Balance Sheet Events
Securities Purchase Agreement
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 (the "Private Placement"). The Private Placement resulted in net proceeds to the Company of approximately $144.0 million after deducting placement agent fees. 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.

Going Concern

At 31 December 2020, the Group held cash, cash equivalents and marketable securities of $191.9 million, and the Company held cash and marketable securities of $134.6 million. The directors have prepared a forecast through 2022 and expect that its cash, cash equivalents, and marketable securities on hand as of December 31, 2020 of $191.9 million, together with the proceeds from the Private Placement of $150.0 million of ordinary shares that closed in February 2021 (see "Post Balance Sheet Events" section above), will be sufficient to fund its operations and capital expenditure requirements for at least the next twelve months. The directors have considered the effect of the COVID-19 pandemic on our forecast, and have determined it does not have an effect on our ability to operate as a going concern for at least 12 months from the issuance of these consolidated financial statements. Therefore, the directors have at the time of approving the financial statements, a reasonable expectation that the Group and Company has adequate resources to continue in operational existence for the foreseeable future. Accordingly, the Group and Company continues to adopt the going concern basis of accounting in preparing the financial statements.

Employee Involvement

The Company has outlined key human capital disclosures in our Strategic Report on page 82 of this Annual Report.

Greenhouse gas emissions

The Company has outlined its greenhouse gas emissions estimate in the "Environmental Matters" section of the Strategic Report beginning on page 82 of this Annual Report.

Financial Risk Management

Credit and Interest Rate Risk

As of December 31, 2020, we had cash, cash equivalents, marketable securities, and restricted cash of $196.2 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 $25.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 6% plus LIBOR. As of December 31, 2020, the carrying value of the term loans under the credit facility was $25.1 million, $4.9 million of which was classified as a current liability, and $20.2 million of which was classified as a long-term liability.

Liquidity Risk

From our inception through December 31, 2020, 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 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 full, or standard, marketing authorization for Libmeldy. We expect to launch Libmeldy in Europe and generate product sales as early as the first half of 2021. 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 convertible preferred shares, proceeds from share issuances from employee equity plans, receipts from the United Kingdom research and development tax credit,

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"), and our Credit Facility.

On February 27, 2020, we entered into a Sales Agreement with Cowen and Company, LLC, as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. As of December 31, 2020, we have not sold any shares under the Sales Agreement.

Through December 31, 2020, we have received net proceeds of $335.2 million from the sale of ADSs in our initial public offering and follow-on offering, net proceeds of $283.4 million from sales of convertible preferred shares, $24.5 million in net proceeds from our Credit Facility, $33.9 million in receipts associated with our United Kingdom research and development tax credit of , $7.1 million in proceeds from share issuances from employee equity plans, and reimbursement of $8.2 million from our agreement with CIRM, which was formerly a subcontract agreement with UCLA. As of December 31, 2020, we had cash, cash equivalents, and marketable securities of $191.9 million, excluding restricted cash.

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 (the "Private Placement"). The Private Placement resulted in net proceeds to us of approximately $144.0 after deducting placement agent fees. 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.

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 in our consolidated financial statements.

Foreign exchange risk

The Company is exposed to foreign currency exchange risk because it primarily 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 gains of $3.4 million and $1.4 million for the years ended December 31, 2020 and 2019. These foreign currency transaction gains and losses are included in other income (expense) in our consolidated statement of operations and comprehensive loss.

Assets and liabilities have been translated at the exchange rates at the balance sheet date, while revenue and expenses are translated at the average exchange rates over the reporting period and shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net income (loss) but are

included in our foreign 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.

Branches outside of the UK

The following table outlines all subsidiaries of the Parent Company:

Name of Subsidiary	Jurisdiction of Incorporation or Organization
Orchard Therapeutics (Europe) Limited	England and Wales
Orchard Therapeutics North America	California (United States)
Orchard Therapeutics (Netherlands) B.V.	Netherlands
Orchard Therapeutics (France) SAS	France
Orchard Therapeutics (Italy) S.r.l	Italy
Orchard Therapeutics (Germany) GmbH	Germany

Qualifying third party indemnity provisions

The Company has granted a qualifying third-party indemnity to each of its directors against liability in respect of proceedings brought by third parties, which was in force throughout the financial year, and remains in force as at the date of approving the UK Statutory Directors' Report.

Independent Auditors

PricewaterhouseCoopers LLP have expressed their willingness to continue in office as auditors for another year. In accordance with Section 418 of the UK Companies Act 2006, a resolution proposing that PricewaterhouseCoopers LLP be re-appointed as auditors of the Group and Company will be proposed at the Annual General Meeting.

On behalf of the Board of Directors:

Bobby Gaspar
Director
9 April 2021

DIRECTORS' REMUNERATION REPORT

Annual Statement from the Chair of the Compensation Committee

Dear Shareholder,

As the Chair of the Compensation Committee (the "Committee"), I am pleased to present, on behalf of the board of directors (the "Board") of Orchard Therapeutics plc (the "Company" or "Orchard"), the Directors' Remuneration Report for the year ended 31 December 2020 (the "Remuneration Report").

The Company's Remuneration Report, will be subject to an advisory vote at the forthcoming Annual General Meeting on 16 June 2021 (the "AGM").

Introduction

Our executive compensation program seeks to incentivize and reward strong corporate performance. All compensation decisions at Orchard remain aligned to our key principle of paying for performance. Further, as a global biopharmaceutical company with major operations in the United States and Europe we operate within a global marketplace for talent. Given that the market for experienced directors and biopharmaceutical executive talent is very competitive, particularly in the United States, the Committee references the US market as the leading indicator for remuneration levels and practices. This helps attract and retain directors and motivate the superior executive talent needed to successfully manage the Company's complex global operations. Being consistent in this market view of the United States as the primary benchmark for remuneration practices for our Executive and Non-Executive Directors is key for the Company as it builds its global operations in a manner designed to deliver sustainable, long-term growth and shareholder value.

As a Committee, we are also mindful of general UK compensation frameworks and investor guidance in that regard when making decisions on Orchard's executive compensation.

In many respects 2020 was a year of transition for Orchard, with founder, Dr Bobby Gaspar's appointment as CEO and progress against a new strategic plan to realize the potential of the HSC gene therapy approach. This was all undertaken against the external challenge of COVID. We also celebrated successes in respect of Libmeldy's approval in the European Union in December 2020.

Key remuneration decisions for 2020

On 18 March 2020, Bobby Gaspar was appointed as Chief Executive Officer. Dr. Gaspar's annual base salary was increased to £440,000, his target annual bonus opportunity was increased to 60% of his base salary. The Committee reviewed this salary against relevant competitive market data and that of the previous incumbent. In relation to this promotion, Dr. Gaspar was granted an option to purchase 300,000 of the Company's ordinary shares, effective 1 April 2020. In addition, Dr. Gaspar was awarded 195,000 Performance Share Units (PSUs) subject to the achievement of specific clinical and regulatory milestones before 31 December 2023.

2020 Annual Bonus

Consistent with prior years, the annual bonus for 2020 was based upon our stated corporate objectives. These make up a scorecard of the research, clinical, commercial and operational goals which ultimately drive long-term, sustainable and strategic success of the Company. For the Executive Team, the Committee determined a performance score of 100% of target. This reflects the strong performance against the corporate objectives. Details of the Company's performance against these goals are described in the main body of this report. For 2020, this represents a bonus of 60% salary for the CEO. As a Committee, we made the decision to reduce the cash payment of executive bonuses and deliver only one half in cash. The remaining half of the executive bonus was an additional award of share options granted in lieu of this portion of the bonus, with the number of options calculated on a fair value basis. The cash portion of the bonuses that were replaced by share options was added to the all employee bonus pool and facilitated increased bonus awards within the Company.

Remuneration for 2021

There are no substantial changes to our approach to executive compensation for 2021. No increase to Dr. Gaspar's salary was made for 2021 and his bonus target remains at 60% salary. Consistent with our pay for performance philosophy, Dr. Gaspar was granted an annual award of share options in February 2021 alongside an additional option award as part of the bonus arrangement above.

Changes to the Board

Mr. Rothera stepped down from his position as President and Chief Executive Officer and resigned as a director of the Company on 17 March 2020. Details of his compensation on termination can be found in this report.

Steven Altschuler was appointed as a Non-Executive Director of the Company, effective as of 3 February 2020. We welcome him to the Board where he also serves on the Board's Science and Technology Committee.

Conclusion

The Committee believes that the Directors' Remuneration Policy has been implemented fairly and consistently, as described in this report, and that it will continue to properly motivate our Executive Directors to deliver sustainable growth and shareholder value over the long term and to do so in a responsible and cost-efficient manner.

I hope that you find the information in this report helpful, and I look forward to your support at the Company's AGM.

Yours sincerely,

Charles Rowland, Jr.
Chair of the Compensation Committee

9 April 2021

Remuneration Policy

This part of the Directors' Remuneration Report sets out the remuneration policy for the Company. The current Directors' Remuneration Policy (the "Policy") was put forward for approval by shareholders in a binding vote at the AGM on 26 June 2019 and approved with a majority of 91.6% vote in favour of taking effect from the date of approval and applying for a period of three years until 2022.

Key considerations when determining the Remuneration Policy

The Policy was designed by the Committee with a number of specific principles in mind:

- attract, retain and motivate high calibre senior management and focus them on the delivery of the Company's strategic and business objectives;
- encourage a corporate culture that promotes the highest level of integrity, teamwork and ethical standards;
- be competitive against appropriate market benchmarks (being predominantly the US biotech sector) and have a strong link to performance, providing the ability to earn above-market rewards for strong performance;
- be simple and understandable, both internally and externally;
- encourage increased equity ownership to motivate executives in the overall interests of shareholders, the Company, employees and customers; and
- take due account of good governance and promote the long-term success of the Company.

In seeking to achieve the above objectives, the Committee is mindful of the views of a broad range of stakeholders in the business and accordingly takes account of a number of factors when setting remuneration including: market conditions; pay and benefits in relevant comparator organisations; terms and conditions of employment across the Company; the Company's risk appetite; the expectations of institutional shareholders; and any specific feedback received from shareholders and other stakeholders.

Remuneration Policy table

The table in the following pages sets out, for each element of pay, a summary of how remuneration is structured and how it supports the Company's strategy.

Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
Base salary To recruit and retain Executive Directors of the highest calibre who are capable of delivering the Company's strategic objectives, reflecting the individual's experience and role within the Company. Base salary is designed to provide an appropriate level of fixed income to avoid any over-reliance on variable pay elements that could encourage excessive risk taking.	Salaries are normally reviewed annually, and changes are generally effective from 1 January each year. The annual salary review for Executive Directors takes a number of factors into consideration, including: • business performance; • salary increases awarded to the overall employee population; • skills and experience of the individual over time; • scope of the individual's responsibilities; • changes in the size and complexity of the Company; • market competitiveness assessed by periodic benchmarking; and • the underlying rate of inflation.	Whilst there is no prescribed formulaic maximum, any increases will take into account prevailing market and economic conditions and the approach to employee pay throughout the organisation. Base salary increases are awarded at the discretion of the Committee; however, salary increases will normally be no greater than the general increase awarded to the wider workforce, in percentage of salary terms. However, a higher increase may be made where an individual had been appointed to a new role at below- market salary while gaining experience. Subsequent demonstration of strong performance may result in a salary increase that is higher than that awarded to the wider workforce.	Executive Directors' performance is a factor considered when determining any salary increases.

Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
Benefits Reasonable benefits-in-kind are provided to support Executive Directors in carrying out their duties and assist with retention and recruitment.	The Company aims to offer benefits that are in line with market practice. The main benefits currently provided include private health insurance, long-term disability, critical illness and death in service. Under certain circumstances the Company may offer relocation allowances or assistance. Expatriate benefits may be offered where required. Travel and any reasonable business- related expenses (including tax thereon) may be reimbursed. Executive Directors may become eligible for other benefits in future where the Committee deems it appropriate. Where additional benefits are introduced for the wider workforce, Executive Directors may participate on broadly similar terms.	The value of each benefit is not predetermined and is typically based upon the cost to the Company of providing said benefit.	Not performance related.
Pensions The Company aims to provide a contribution towards life in retirement.	Executive Directors are eligible to receive employer contributions to the Company's Group Personal Pension Scheme or to a 401k plan or a salary supplement in lieu of pension benefits, or a mixture of both.	Up to 6% of salary per annum for Executive Directors.	Not performance related.

Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
Annual bonus The annual bonus scheme rewards the achievement of stretching objectives that support the Company's corporate goals and delivery of the business strategy.	Bonuses are determined based on measures and targets that are agreed by the Committee at the start of each financial year.	The maximum target bonus opportunity for Executive Directors is 80% of salary, with a maximum bonus opportunity of up to two times the target opportunity. For threshold performance, no more than 50% of target bonus may be payable. For 2021, the target bonus opportunity for Executive Directors will be no more than 60% of salary, with a maximum bonus opportunity of up to 150% of the target opportunity.	Performance measures are determined by the Committee each year and may vary to ensure that they promote the Company's business strategy and shareholder value. The annual bonus will be based on strategic goals, which may include financial, strategic and personal objectives. The Committee may alter the bonus outcome if it considers that the pay-out is inconsistent with the Company's overall performance, taking account of any factors it considers relevant. This will help ensure that pay-outs reflect overall Company performance during the year.

Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
2018 Share Option and Incentive Plan ("SOIP")			
The SOIP is designed to incentivise the successful execution of business strategy over the longer term and provide long-term retention. Facilitates share ownership to provide further alignment with shareholders.	The Committee will select the most appropriate form of SOIP award(s) each year. Awards will typically be granted annually, in the form of options and restricted share units ("RSUs") although may also be granted in the form of share appreciation rights, restricted shares, unrestricted shares, performance share units, cash or dividend equivalent rights. Currently, options normally vest over a period of four years on a monthly basis. Initial grants generally vest 25% after one year, and monthly thereafter for 36 months. Currently, time-based RSUs normally vest in equal installments annually over a three-year vesting term. PSUs normally vest in three equal tranches on the meeting of agreed milestone events within a period of three years. The Committee may vary the vesting schedule of future grants of options and PSUs as it considers appropriate. At the discretion of the Committee, participants may also be entitled to receive the value of dividends paid between grant and vesting on vested shares. The payment may be in cash or shares and may assume dividend reinvestment.	There is no defined maximum opportunity under the SOIP. However, the Committee will generally work within the guidelines provided by our compensation consultants. We seek to establish equity-based remuneration competitive to that offered by a set of comparable companies with whom we may compete for talent.	Performance conditions may apply to awards. Such conditions may be strategic objectives which may include milestone events, financial, strategic and/or personal objectives. Share options are granted with an exercise price no less than the fair market value of the shares on the date of grant. Accordingly, share options will only have value to the extent the Company's share price appreciates following the date of grant. Any performance conditions set will be designed to incentivise performance in support of the Company's strategy and business objectives. The Committee has flexibility to vary the mix of measures or introduce new measures for each subsequent award taking into account business priorities at the time of grant. The Committee may alter the vesting outcome if it considers that the level of vesting is inconsistent with the underlying performance of the business, taking account of any factors it considers relevant. This will help ensure that vesting reflects overall Company performance during the year.

Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
Employee Stock Purchase Plan ("ESPP")			
Encourages employee share ownership and therefore increases alignment with shareholders.	The Company operates an employee share purchase plan that offers employees the opportunity to purchase shares in the Company through payroll deductions at a price equal to 85% of the lower of fair market value of the shares on the first business day or the last business day of the offering period. The ESPP is available to all employees whose customary employment is for more than 20 hours per week and have completed at least 30 days of employment.	Employees may contribute up to 15% of their base compensation to purchase shares under the ESPP. However, the right to purchase shares under the ESPP may not accrue at a rate that exceeds $25,000 worth of ordinary shares, valued at the start of the purchase period, under the ESPP, for each calendar year in the purchase period.	Not performance related.

Non-Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
Fees To attract Non-Executive Directors who have a broad range of experience and skills to provide independent judgement on issues of strategy, performance, resources and standards of conduct.	Non-Executive Directors receive an annual retainer paid in cash, comprising a base fee plus additional fees for additional responsibilities, such as a Committee Chairpersonship or membership and the role of Chairperson. The Chair's fee is reviewed annually by the Committee (without the Chair present). Fee levels for the Non-Executive Directors are determined by the Company Chair and Executive Directors. When reviewing fee levels, account is taken of market movements in fee levels, Board committee responsibilities, ongoing time commitments and the general economic environment. In exceptional circumstances, if there is a temporary yet material increase in the time commitments for Non-Executive Directors, the Board may pay additional fees to recognise that additional workload. Non-Executive Directors ordinarily do not participate in any pension, bonus or performance- based share incentive plans. Travel, accommodation and other business- related expenses incurred in carrying out the role will be paid by the Company including, if relevant, any gross-up for tax.	When reviewing fee levels, account is taken of market movements in the fees of Non-Executive Directors, Board Committee responsibilities and ongoing time commitments, as well as the underlying rate of inflation. Actual fee levels are disclosed in the annual Directors' Remuneration Report for the relevant financial year.	Not performance related.

Non-Executive Directors

Purpose and link to strategy	Operation	Maximum opportunity	Performance metrics
Equity Awards To facilitate share ownership and provide alignment with shareholders.	Non-Executive Directors may receive an equity award in the form of options, share appreciation rights, restricted shares, restricted share units or such other form permitted under the SOIP. New Non-Executive Directors receive an initial equity award upon appointment or election. In addition, Non-Executive Directors receive annual equity awards at the time of the annual meeting. Currently any initial equity awards normally vest in equal monthly installments for 36 months, and any annual awards normally are awarded at the AGM and vest at the earlier of the next AGM or one year after the grant date.	There is no maximum award level for equity awards to Non- Executive Directors. The size of the equity awards is determined by the full Board of Directors, upon recommendation of the Compensation Committee. When reviewing award levels, account is taken of market movements in equity awards, Board committee responsibilities, ongoing time commitments and the general economic conditions.	Not performance related.

Notes to the policy table

Legacy arrangements

For the duration of this Policy, the Company will honour any commitments made in respect of current or former Directors before the date on which either: (i) the Policy becomes effective; or (ii) an individual becomes a Director, even where not consistent with the Policy set out in this report or prevailing at the time such commitment is fulfilled. For the avoidance of doubt, all outstanding historic awards that were granted in connection with, or prior to, listing remain eligible to vest based on their original or modified terms.

Performance conditions

The choice of annual bonus performance metrics reflects the Committee's belief that any incentive remuneration should be appropriately challenging and tied to the delivery of key strategic objectives intended to ensure that Executive Directors are incentivised to deliver across a range of objectives for which they are accountable. The Committee has retained flexibility on the specific measures which will be used to ensure that any measures are fully aligned with the strategic imperatives prevailing at the time they are set.

The targets for the bonus scheme for the forthcoming year will be set out in general terms, subject to limitations with regards to commercial sensitivity. The full details of the targets will be disclosed when they are in the public domain and are no longer considered commercially sensitive.

Where used, performance conditions applicable to SOIP awards will be aligned with the Company's objective of delivering superior levels of long-term value to shareholders. The full details of performance conditions will be disclosed when they are in the public domain and are no longer commercially sensitive. Prior to each award, the Committee has flexibility to select measures that are fully aligned with the strategy prevailing at the time awards are granted.

The Committee will review the calibration of targets applicable to the annual bonus, and the SOIP in years where performance measures apply, annually to ensure they remain appropriate and sufficiently challenging, taking into account the Company's strategic objectives and the interests of shareholders.

Differences in remuneration policy between Executive Directors and other employees

The overall approach to reward for employees across the workforce is a key reference point when setting the remuneration of the Executive Directors. When reviewing the salaries of the Executive Directors, the Committee pays close attention to pay and employment conditions across the wider workforce and in normal circumstances the increase for Executive Directors will be no higher than the average increase for the general workforce.

The key difference between the remuneration of Executive Directors and that of our other employees is that, overall, at senior levels, remuneration is increasingly long-term, and 'at risk' with an emphasis on performance-related pay linked to business performance and share-based remuneration. This ensures that remuneration at senior levels will increase or decrease in line with business performance and provides alignment between the interests of Executive Directors and shareholders. In particular, long-term incentives are provided only to the most senior executives as they are reserved for those considered to have the greatest potential to influence overall levels of performance.

Committee discretion in operation of variable pay schemes

The Committee operates under the powers it has been delegated by the Board. In addition, it complies with rules that are either subject to shareholder approval or by approval from the Board. These rules provide the Committee with certain discretions which serve to ensure that the implementation of the remuneration policy is fair, both to the individual Director and to the shareholders. The Committee also has discretions to set components of remuneration within a range, from time to time. The extent of such discretions is set out in the relevant rules, the maximum opportunity or the performance metrics section of the policy table above. To ensure the efficient administration of the variable incentive plans outlined above, the Committee will apply certain operational discretions.

These include the following:

- selecting the participants in the plans on an annual basis;
- determining the timing of grants of awards and/or payments;
- determining the quantum of awards and/or payments (within the limits set out in the policy table above);
- determining the choice (and adjustment) of performance measures and targets for each incentive plan in accordance with the policy set out above and the rules of each plan;
- determining the extent of vesting based on the assessment of performance and discretion relating to measurement of performance in certain events such as a change of control or reconstruction;
- making the appropriate adjustments required in certain circumstances, for instance for changes in capital structure;

- determining "good leaver" status, if applicable, for incentive plan purposes and applying the appropriate treatment; and
- undertaking the annual review of weighting of performance measures and setting targets for the annual bonus plan and other incentive schemes, where applicable, from year to year.

If an event occurs which results in the annual bonus plan or SOIP performance conditions and/or targets being deemed no longer appropriate (e.g. material acquisition or divestment), the Committee will have the ability to make appropriate adjustments to the measures and/or targets and alter weightings, provided that the revised conditions are not materially less challenging than the original conditions. Any use of the above discretion would, where relevant, be explained in the Annual Report on Remuneration and may, as appropriate, be the subject of consultation with the Company's major shareholders.

Shareholder views

The Board is committed to dialogue with shareholders and intends to engage directly with them and their representative bodies when considering any significant changes to our remuneration arrangements. The Compensation Committee will consider shareholder feedback received following the AGM, as well as any additional feedback and guidance received from time to time. This feedback will be considered by the Committee as it develops the Company's remuneration framework and practices going forward. Assisted by its independent adviser, the Compensation Committee also actively monitors developments in the expectations of institutional investors and their representative bodies.

Employment conditions

The Committee is regularly updated throughout the year on pay and conditions applying to Company employees. Where significant changes are proposed to employment conditions elsewhere in the Company these are highlighted for the attention of the Committee at an early stage.

Other remuneration policies

Remuneration for new appointments

Where it is necessary to appoint or replace an Executive Director or to promote an existing Executive Director, the Committee's approach when considering the overall remuneration arrangements in the recruitment of a new Executive Director is to take account of the calibre, expertise and responsibilities of the individual, his or her remuneration package in their prior role and market rates. Remuneration will be in line with our policy and the Committee will not pay more than is necessary to facilitate their recruitment.

The remuneration package for a new Executive Director will be set in accordance with the terms of the Company's approved remuneration policy in force at the time of appointment. Further details are provided below:

Salary	The Committee will set a base salary appropriate to the calibre, experience and responsibilities of the new appointee. In arriving at a salary, the Committee may take into account, amongst other things, the market rate for the role and internal relativities.

	The Committee has the flexibility to set the salary of a new Executive Director at a lower level initially, with a series of planned increases implemented over the following few years to bring the salary to the desired positioning, subject to individual performance. In exceptional circumstances, the Committee has the ability to set the salary of a new Executive Director at a rate higher than the market level to reflect the criticality of the role and the experience and performance of the individual.
Benefits	Benefits will be consistent with the principles of the policy. The Company may award certain additional benefits and other allowances including, but not limited to, those to assist with relocation support, temporary living and transportation expenses, educational costs for children and tax equalisation to allow flexibility in employing an overseas national.
Pension benefits	A maximum pension contribution of 6% of salary may be payable for external appointments. For an internal appointment, his or her existing pension arrangements may continue to operate. Any new Executive Director based outside the UK will be eligible to participate in pension or pension allowance, insurance and other benefit programmes in line with local practice.
Annual bonus	The maximum bonus opportunity for new appointments is 150% of their target bonus.
Other cash or equity-based awards	Executive Directors may receive awards under the SOIP on appointment. The Committee will assess and determine the award level, award vehicle, performance conditions and vesting schedule for each individual on a case-by-case basis. In addition, Executive Directors are eligible to participate in the ESPP subject to the conditions set forth therein. In addition, the Committee may offer additional cash and/or equity-based elements in order to "buy-out" remuneration relinquished on leaving a former employer. Any awards made in this regard may have no performance conditions, or different performance conditions, or a different vesting schedule compared to the Company's existing plans, as the Committee considers appropriate. Depending on the timing and responsibilities of the appointment, it may be necessary to set different annual bonus or SOIP performance measures and targets as applicable to other Executive Directors.

The terms of appointment for a Non-Executive Director would be in accordance with the remuneration policy for Non-Executive Directors as set out in the policy table.

Service contracts and termination policy

Executive Directors have rolling service agreements which may be terminated in accordance with the terms of these agreements. The period of notice for Executive Directors will not normally exceed 12 months. Executive Directors' service agreements are available for inspection at the Company's registered office during normal business hours.

Name	Position	Date of service contract	Notice period
Bobby Gaspar	Chief Executive Officer	2 January 2018	6 months either party

The Company's policy on remuneration for Executive Directors who leave the Company is set out below. The Committee will exercise its discretion when determining amounts that should be paid to leavers, taking into account the facts and circumstances of each case. Generally, in the event of termination, the Directors' service contracts may provide for payment of basic salary over the notice period. Where applicable, the Company may elect to make a payment in lieu of notice (PILON) equivalent in value to basic salary for any unexpired portion of the notice period. PILON payments may be made in monthly instalments or as a lump sum, and the individual is expected to take reasonable steps to seek alternative income to mitigate the payments. The Company may also pay for outplacement services for Executive Directors on termination or the Company may elect to make a payment in lieu of outplacement services. The Company may continue to pay the employer health plan premium for the Executive Director on termination for a period of up to 12 months (up to 18 months in connection with a change in control).

Any outstanding incentive awards will be treated in accordance with the plan rules, as follows:

	Termination without cause or for cause by participant	Termination for cause	Termination without cause or for cause by participant in connection with change of control
Salary	A payment equal to up to 12 months' salary payable as a lump sum or on a monthly basis, less any amounts payable pursuant to any restrictive covenant agreements (if applicable) ("Restrictive Covenants Agreement Setoff") paid or to be paid in the same calendar year.	No payment.	A payment of up to 18 months' salary payable as a lump sum or on a monthly basis for termination without cause, less any Restrictive Covenants Agreement Setoff (if applicable) paid or to be paid in the same calendar year.
Annual Bonus	Unpaid annual cash bonus in respect of prior year performance, which otherwise would have been earned if participant had remained employed through the payment date, should be paid in full. A pro-rata amount of the participant's target bonus for the current year should be paid, subject to the participant's actual performance.	Unpaid annual cash bonuses lapse in full.	Up to 1.5 times the participant's target bonus may be payable less any Restrictive Covenants Agreement Setoff (if applicable) paid or to be paid in the same calendar year.

	Termination without cause or for cause by participant	Termination for cause	Termination without cause or for cause by participant in connection with change of control
Share Option Incentive Plan	Unvested awards lapse in full, except where the participant leaves in circumstances where they retain a statutory right to return to work (in which case, awards will continue to vest on normal terms).	Unvested awards lapse in full.	On a change of control, merger, reorganization or other corporate event, the Company may seek to replace awards with new awards in the successor company (to the extent agreed with the successor company). In the case of a termination without cause or for cause by the participant in connection with a change of control, such awards will accelerate and vest in full. Where there is no agreement to replace awards, on a corporate event awards with time-based vesting conditions shall vest on the date of that event and awards with performance-based vesting conditions shall vest on the date of that event to the extent determined by the Company (regardless of the extent to which any performance conditions attached to awards have been satisfied).

The Company is unequivocally against rewards for failure; the circumstances of any departure, including the individual's performance, would be taken into account in every case. Statutory redundancy payments may be made, as appropriate. Service agreements may be terminated summarily without notice (or on shorter notice periods) and without payment in lieu of notice in certain circumstances, such as gross misconduct or any other material breach of the obligations under their employment contract. The Company may require the individual to work during their notice period or may place them on garden leave during which they would be entitled to salary, benefits and pension only.

Except in the case of gross misconduct or resignation, the Company may at its absolute discretion reimburse for reasonable professional fees relating to the termination of employment and, where an Executive Director has been required to re-locate, to pay reasonable repatriation costs, including possible tax exposure costs. This includes any statutory entitlements or sums to settle or compromise claims in connection with a termination (including, at the discretion of the Committee, reimbursement for legal advice and provision of outplacement services).

Policy on external appointments

The Board believes that it may be beneficial to the Company for executives to hold non-executive directorships outside the Company. Any such appointments are subject to approval by the Board, and the director may retain any fees received at the discretion of the Board. Dr Gaspar does not currently hold any outside directorships.

Non-Executive Directors' terms of engagement

Each of the Non-Executive Directors is engaged under a Non-Executive Director appointment letter. In any event, each appointment is terminable by either party on not less than three months' written notice. Our board of directors is classified, meaning that each of our directors is designated to one of three classes and is elected to serve a term of between one and three years. The Chair and Non-Executive Directors are only entitled to fees accrued to the date of termination.

The dates of appointment of each of the Non-Executive Directors serving at 31 December 2020 are summarised in the table below. Dates prior to our incorporation in August 2018 as Orchard Rx Limited (now known as Orchard Therapeutics plc) are for Non-Executive Directors who served on the board of our predecessor company, Orchard Therapeutics Limited (now known as Orchard Therapeutics (Europe) Limited).

Non-Executive Directors	Date of contract or date of appointment
Joanne Beck	1 July 2018
Marc Dunoyer	6 June 2018
Jon Ellis	17 July 2018
James Geraghty	4 June 2018
Charles Rowland	1 June 2018
Alicia Secor	7 December 2018
John Curnutte	30 August 2019
Steven Altschuler	3 February 2020

Directors' letters of appointment are available for inspection at the Company's registered office during normal business hours and will be available for inspection at the AGM.

Annual Report on Remuneration

This part of the report has been prepared in accordance with Part 3 of The Large and Medium-sized Companies and Groups (Accounts and Reports) (Amendment) Regulations 2013 as amended and Rule 9.8.6 of the Listing Rules. Since the Company is not FTSE-listed, it is under no obligation to comply with the UK Corporate Governance Code, but best practice and good governance have been considered when preparing this report. The Annual Report on Remuneration and the Annual Statement by the Chair of the Compensation Committee will be put to a single advisory shareholder vote at the AGM on 16 June 2021.

Compensation Committee (the "Committee")

The current members of the Committee, who are all independent, are Charles Rowland (Chair), Joanne Beck and Alicia Secor.

The Company Chair and members of management are invited to attend meetings where appropriate. The Company Secretary is the secretary to the Committee. Attendees are not involved in any decisions and are not present for any discussions regarding their own remuneration.

No conflicts of interest have arisen during the period and none of the members of the Committee has any personal financial interest in the matters discussed, other than as shareholders. The fees of the Non-Executive Directors are approved by the Board on the joint recommendation of the Committee and the Executive Directors.

Meetings attendance during 2020

	Attendance
Charles Rowland	10 of 10
Joanne Beck	10 of 10
Alicia Secor	10 of 10

Independent advisors

Wholly independent advice on executive remuneration is received from the Executive Compensation practice of Aon plc.. Aon advises on remuneration arrangements and all aspects of senior executive remuneration. In 2020, Aon assisted the Committee and kept the Committee up to date on remuneration trends. During the 2020 financial year, fees charged by Aon for advice provided to the Committee for 2020 amounted to $171,329 (excluding VAT). In addition, Aon provided advice to the Company's Human Resources function on implementation, which the Committee considers in no way prejudices Aon's position as the Committee's independent advisor. Goodwin Procter LLP have also advised the Company's Human Resources function on compensation.

Activity in the period

The Committee's principal function is to support Orchard's strategy by ensuring that those individuals responsible for delivering the strategy are appropriately incentivised and rewarded through the operation of Orchard's remuneration policy. In implementing the remuneration policy, and in constructing the remuneration arrangements for executive directors and senior employees, the Board, advised by the Committee, aims to provide remuneration packages that are competitive and designed to attract, retain and motivate Executive Directors and senior employees of the highest calibre.

The Committee is responsible for and considered, where applicable, during the period:

- evaluating the efficacy of the Company's remuneration policy and strategy;
- reviewing and determining remuneration to be paid to the Company's executive officers and directors;
- reviewing and making recommendations to the Board regarding remuneration for non-executive members of the Board;
- agreeing the design of all share incentive plans;
- prepare any report on executive remuneration required by the rules and regulations of the US Securities and Exchange Commission, The Nasdaq Stock Market LLC and as required under UK law;
- reviewing, evaluating, and approving employment agreements, severance agreements, change-of-control protections, corporate performance goals and objectives, and other compensatory arrangements of the executive officers and other senior management and adjusting remuneration, as appropriate;
- evaluating and approving remuneration plans and programs and establishing equity remuneration policies;
- reviewing remuneration practices and trends to assess the adequacy and competitiveness of the executive remuneration programs as compared to industry peers, and determining the appropriate levels and types of remuneration to be paid;

- approving any loans by the Company to employees;
- reviewing and approving remuneration arrangements for any executive officer involving any subsidiary, special purpose or similar entity, with consideration of the potential for conflicts of interest; and
- reviewing the Company's practices and policies of employee remuneration as they relate to risk management and risk-taking incentives.

The Committee is formally constituted and operates on written terms of reference, which are available on Orchard's website, www.orchard-tx.com.

Statement of shareholder voting at 2020 AGM

At last year's AGM held on 17 June 2020, votes cast by proxy and at the meeting in respect of the Directors' remuneration were as follows:

	Votes For		Votes Against		Votes Withheld	
	% of votes cast	Number of votes	% of votes cast	Number of votes	% of votes cast	Number of votes
To approve the Directors' Remuneration Report	99.8%	84,377,519	0.1%	122,320	0.1%	54,055

The Directors' Remuneration Policy was approved the Company's AGM held on 26 June 2019 as follows:

	Votes For		Votes Against		Votes Withheld	
	% of votes cast	Number of votes	% of votes cast	Number of votes	% of votes cast	Number of votes
To approve the Directors' Remuneration Policy	91.6%	33,863,941	8.4%	3,110,196	0%	750

Single total figure of Directors' remuneration – year ended 31 December 2020 (audited)

The total remuneration of the individual Directors who served in the year ended 31 December 2020, is shown below. Total remuneration is the sum of emoluments plus Company pension contributions. The below table has been presented in US dollars ($) which is the functional currency of the reporting entity:

		Base salary /fees $000	Benefits[2] $000	Pension $000	Bonus $000	SOIP[3] $000	PSUs[4] $000	Other[5] $000	Total remun-eration $000	Total fixed	Total variable
Executive Directors											
Bobby Gaspar[1]	2020	542.5	6.6	–	169.9	–	44.8	–	763.8	549.1	214.7
	2019	344.0	–	–	174.0	–	–	–	518.0	344.0	174.0
Mark Rothera[6]	2020	160.2	14.3	11.4	–	–	–	–	186.0	186.0	–
	2019	527.0	32.0	11.0	369.0	–	–	77.0	1016.0	570.0	446.0
Non-Executive Directors											
Steven Altschuler[7]	2020	47.2	–	–	–	–	–	–	47.2	47.2	–
	2019	–	–	–	–	–	–	–	–	–	–
Joanne Beck	2020	58.0	–	–	–	–	–	–	58.0	58.0	–
	2019	41.0	–	–	–	–	–	–	41.0	41.0	–
John Curnutte	2020	60.5	–	–	–	–	–	–	60.5	60.5	–
	2019	16.0	–	–	–	–	–	–	16.0	16.0	–
Marc Dunoyer	2020	59.5	–	–	–	–	–	–	59.5	59.5	–
	2019	47.0	–	–	–	–	–	–	47.0	47.0	–
Jon Ellis	2020	–	–	–	–	–	–	–	–	–	–
	2019	–	–	–	–	–	–	–	–	–	–
James Geraghty	2020	95.8	–	–	–	–	–	–	95.8	95.8	–
	2019	83.0	–	–	–	–	–	–	83.0	83.0	–
Charles Rowland	2020	78.7	–	–	–	–	–	–	78.7	78.7	–
	2019	60.0	–	–	–	–	–	–	60.0	60.0	–
Alicia Secor	2020	53.0	–	–	–	–	–	–	53.0	53.0	–
	2019	43.0	–	–	–	–	–	–	43.0	43.0	–
Total	2020	1155.4	20.9	11.4	169.9	–	44.8	–	1402.4	1187.7	214.7
	2019	1161.0	32.0	11.0	543.0	–	–	77.0	1824.0	1204.0	620.0

1. Dr Gaspar's salary was £356,700 until March. On appointment to CEO, his salary was increased to £440,000. This is converted at a 12-month average rate for 2020 of USD 1 = GBP 1.287.
2. For Executive Directors, included private health insurance, long term disability, critical illness and death in service benefits. Mark Rothera received a housing allowance until he resigned from the Company.
3. The figures for the SOIP represent the intrinsic value of the share options on the date of grant. All share options granted to Directors are awarded at the market value and therefore the intrinsic value at the time of grant is zero. Details of all options awarded to individual Directors during the year, including the number of options under award, the exercise price, vesting schedule and the grant date fair value can be found in the tables below. All awards in the column are subject to continued service only and are not subject to any further performance conditions.
4. 6,250 PSUs vested as a result of Libmeldy's approval by the European Commission on the 17 December 2020. These shares vested on 8 January 2021 and are valued using the closing price of $7.17. None of this value was attributable to share price appreciation from the time of grant.
5. Other expenses include payments for relocation/housing benefits and tax-related services.
6. Mr Rothera ceased to be a Director of the Company of 17 March 2020. Payments made to Mr Rothera for his loss of office are disclosed later in this report.
7. Steven Altschuler joined the Board of Directors on 3 February 2020.

2020 Annual bonus (audited)

During a series of meetings in December 2020 and January 2021, the Compensation Committee evaluated achievement of the 2020 corporate objectives and each Executive Director's individual performance.

The Compensation Committee reviewed the corporate goals, below, and based on the results approved a 100% achievement level of the 2020 corporate objectives.

Key achievements against agreed goals were as follows:

Transition Lead Programs into Approved Therapies – most significantly during the year was the receipt in December of MAA approval from the European Commission for OTL-200 (MLD) – Libmeldy™. This is an important and significant achievement for Orchard. Also for OTL-200, an IND was filed with the request for RMAT designation in the US. Substantial work and progress was made aligning with the FDA on the current clinical dataset for OTL-103 (WAS) which will inform the path to a BLA submission.

Build a World-leading Gene Therapy Pipeline – 2020 saw important steps taken in both OTL-203 (MPS-I) and OTL -201 (MPS-IIIA). For OTL-203 interim data in the proof-of-concept study in the first 8 patients in conjunction with TIGET/OSR was presented at ASGCT meeting in April 2020 and EBMT meeting in August 2020. We also finalized and submitted a protocol for the registrational study for scientific advice. For OTL 201, three patients were enrolled in proof-of-concept study and data on first patient was presented by a University of Manchester investigator at ASH meeting in December 2020.

Generate Competitive Advantage with our CMC Platform – important achievements in the year included the signing of a stable cell line licence for TDT and WAS (July 2020) as well as the identification of a drug product CDMO partner in the U.S. to initiate technology transfer process. Further, a transduction enhancer combination was identified that delivers at least 50% reduction in vector requirement at research scale.

Achieve Financial Targets & Position for Strong Commercial Launch – in relation to Libmeldy, a new-born screening pilot was initiated in the U.S. and one in Europe for Libmeldy with contracts executed in New York (US) and Germany (EU) in addition to pricing corridor and access strategy in the EU and the establishment of an operational launch structure in EU countries, Middle East & Turkey.

Financially, the business operated within approved limits relative to cash runway and achieved revenue targets. As noted, 2020 saw a successful leadership transition and implementation of refreshed organisational culture across Orchard.

Additional achievements and considerations
Further to the stated corporate goals as approved by the Board for 2020, the Company also achieved a number of incremental accomplishments in relation to the product pipeline and corporate activities. The Compensation Committee considered these in making the final bonus decisions for 2020.

Achievements included PRIME designation for OTL-203 (MPS-I), nine accepted abstracts at the WORLD symposium (presented in February 2021) and filed patent applications for proprietary HAE and FTD programs.

In evaluating the Company's performance the Committee noted the significant challenges that the business has overcome during the year. These include, but not limited to, the leadership changes and transition of CEO from Mr Rothera to Dr Gaspar, and staffing changes in relation to our site in Menlo Park, California.

Additionally, the Committee commends the Company's adaptability and management's leadership in operating remotely as a result of the COVID-19 pandemic.

Delivery of the bonus
A Corporate Performance Score of 100% corresponding to a bonus outcome equivalent to 100% of target for the CEO. The Committee further resolved to deliver 50% of this bonus in cash and 50% as a share option equity award.

An award of additional options was then granted to Dr Gaspar in February 2021. This was consistent with bonuses for Orchard's Executive Leadership Team. The number of share options granted to executives was determined based on the remaining value of the bonus (ie - 50%) and the fair value of the share options. The share options vest over a one-year period on a monthly basis.

The Committee notes that the cash saving made by the Company as a result of this decision was used as additional funding to the available employee bonus pool.

The table below sets forth the 2020 annual base salaries, target annual cash bonus and, the 2020 annual cash bonus earned by Dr Gaspar.

Executive Director	Base salary ($)	Target Annual Cash Bonus (% of salary)	Corporate performance	Cash payment % salary	Cash outcome ($)
Bobby Gaspar	$566,280	60%	100%	30%	$169,897

1 Dr. Gaspar's base salary and bonus are paid in GBP (£) and awards have been translated into USD at a rate of £1.00 =$1.2871, which was the average rate during 2020. The salary basis for the bonus was Dr Gaspar's salary as CEO, £440,000.

Mr. Rothera was paid a pro-rata bonus for the period served in the year until 17 March 2020. Details of this bonus can be found in the Payments for Loss of Office section, below.

Share Option Incentive Plan

Awards granted to Executive Directors in 2020 (audited)

During 2020, Dr Gaspar received three equity awards. The first in January 2020 was an annual award of share options in his role of Chief Scientific Officer.

Additionally, upon his promotion, Bobby Gaspar was granted PSUs and share options as follows:

Executive Director	Form of Award	Date of Grant	Shares Covered	Exercise Price	Face Value at Date of Grant (000)	Fair Value at Date of Grant (000)	Expiry Date	Vest Terms	Vested (as at 31.12.20)	Exercised	Value realized at exercise or vesting	Unexe-rcised
Bobby Gaspar	FMV Options*(1)	02 Jan 2020	200,000	$13.58	$2,716	$1,729	01 Jan 2030	(1)	45,833	Nil	Nil	154,167
Bobby Gaspar	PSU**	01 April 2020	195,000	N/A	$1,375	$0	02 Jan 2024	(2)	Nil	Nil	N/A	N/A
Bobby Gaspar	FMV Options*(3)	01 April 2020	300,000	$7.05	$2,115	$1,316	31 March 2030	(3)	50,000	Nil	Nil	250,000

* The fair market value options are granted at the market price which is the exercise price. The face value at date of grant is calculated as the number of shares multiplied by the exercise price. The fair value at date of grant is calculated as the Black Scholes value.

** The fair value on date of grant for the PSU is based on the market price on the date of grant. None of the strategic performance conditions, as described below, have been deemed probable and the fair value is considered nil at grant date.

(1) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the vesting commencement date of 2 January 2020.

(2) Bobby Gaspar received a one-time grant of 195,000 PSUs, effective 1 April 2020. This PSU award vests as follows: 1/3 of the PSUs will vest on each of the first three of specific clinical and regulatory milestones achieved, subject to Bobby Gaspar remaining an employee of the Company on the date of achievement and provided that in each case the milestone is achieved on or before 2 January 2024. At this time, specific milestones are considered commercially sensitive. Details of the milestones and performance against them will be disclosed at the appropriate time. Details of these performance conditions are deemed to be commercially sensitive and will be disclosed in due course.

(3) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the vesting commencement date of 1 April 2020.

PSUs Vesting in the period

On 16 January 2019, Dr Gaspar had been granted 18,750 Performance Share Units subject to defined milestones in relation to clinical programs and share-price performance.

On December 17, 2020, the Company received full (standard) market authorization of Libmeldy for the treatment of MLD in all 27 member states of the European Union. As a result of this authorization, and following subsequent ratification by the Board, 1/3rd of the shares under award, 6,250, vested on 8 January 2021 and were released to Dr. Gaspar.

Executive Director	Form of Award	Date of Grant	Shares Covered	Vested due to milestone achievement	Number of shares vesting	Share price on vesting date	Vested Value 8 January 2021
Bobby Gaspar	PSUs	16 January 2019	18,750	1/3rd	6,250	$7.17	$44,812

The remaining 12,500 PSUs remain outstanding and subject to performance conditions and will lapse on 31 December 2021 if these are not satisfied prior to that date.

Mr. Rothera awards under the same scheme on 15 November 2018– 219,922 shares – were forfeited on his cessation of employment.

Mark Rothera separation – Payments for loss of office (audited)

On March 17, 2020, we entered into a Separation Agreement and Release with Mr. Rothera which provides, among other things, that Mr. Rothera would receive (i) salary continuation for 12 months, provided that Mr. Rothera has not breached any of his continuing obligations, (ii) a pro-rated bonus representing Mr. Rothera's 50% target bonus for 2020, (iii) reimbursement of COBRA premiums for health benefit coverage for up to 12 months, in an amount equal to the monthly employer contribution that we would have made to provide health insurance to Mr. Rothera had he remained employed with us, (iv) $15,000 in outplacement benefits, and (v) reimbursement of legal fees up to $5,000 and tax assistance up to $7,500.

The amounts paid to Mr. Rothera under this agreement totalled $562,545, comprised of:

Salary continuation ($417,923), a pro-rated bonus amount for 2020 ($57,150), payment covering unused vacation days ($40,747) tax and legal costs ($12,478). He also received healthcare benefits under COBRA ($19,247) and outplacement benefits ($15,000).

Additionally, all time-based equity awards held by Mr. Rothera that would have vested had Mr. Rothera remained employed with us for an additional 12 months following March 17, 2020 immediately vested and became fully exercisable or non-forfeitable. In addition, any vested options remained exercisable until the earlier of (a) the original expiration date for such vested awards or (b) 12 months after the date of his separation. The unvested options held by Mr. Rothera at the time of his separation were not exercisable, unless a change of control of the Company occurred within three months of his separation. The unvested portion of his options have been terminated and all of his PSUs have been forfeited.

Awards granted to Non-Executive directors between 1 January 2020 and 31 December 2020 (audited)

Non-executive directors received the following option awards during the year, each vesting based on continued employment only (in thousands, except for share and per share amounts):

Executive Director	Form of Award	Date of Grant	Shares Covered	Exercise Price	Face Value at Date of Grant	Fair Value at Date of Grant	Expiry Date	Vest Terms	Vested	Exercised	Value realized at exercise	Unexe-rcised
Steven Altschuler	FMV Options*	3 February 2020	50,000	$12.30	$615	$375	2 February 2030	(2)	13,888	Nil	N/A	50,000
Steven Altschuler	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	N/A	N/A	35,000
Joanne Beck	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	N/A	N/A	35,000
Marc Dunoyer	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	N/A	N/A	35,000
James Geraghty	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	N/A	N/A	35,000
Charles Rowland	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	N/A	N/A	35,000
Alicia Secor	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	N/A	N/A	35,000
Jon Ellis	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A
John Curnutte	FMV Options*	17 June 2020	35,000	$7.81	$273	$167	16 June 2030	(1)	Nil	Nil	N/A	35,000

* The fair market value options are granted at the market price which is the exercise price. The face value at date of grant is calculated as the number of shares multiplied by the exercise price. The fair value at date of grant is calculated as the Black Scholes value.

(1) The options vest, and become exercisable at the earlier of one year from the date of grant or the next AGM.

(2) The options vest, and become exercisable, over a three-year period on a monthly basis commencing upon the one-month anniversary of the grant date.

Jon Ellis received no option grants during the year.

Awards granted to Executive Directors in the year ended 31 December 2019

The table below sets forth the option and PSU awards approved in January 2019 (in thousands, except share and per share amounts):

Executive Director	Form of Award	Date of Grant	Shares Covered	Exercise Price	Face Value at Date of Grant	Fair Value at Date of Grant	Expiry Date	Vest Terms
Mark Rothera	FMV options*	16 Jan 2019	415,000	$12.54	$5,204	$3,330	15 Jan 2029	(1)
Bobby Gaspar	FMV options*	16 Jan 2019	50,000	$12.54	$627	$401	15 Jan 2029	(1)

* The fair market value options are granted at the market price which is the exercise price. The face value at date of grant is calculated as the number of shares multiplied by the exercise price. The fair value at date of grant is calculated as the Black Scholes value.

(1) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the date of grant.

Awards granted to Non-Executive directors between 1 January 2019 and 31 December 2019

Non-executive directors received the following option awards during 2019, each vesting based on continued employment only (in thousands, except for share and per share amounts):

Executive Director	Form of Award	Date of Grant	Shares Covered	Exercise Price	Face Value at Date of Grant	Fair Value at Date of Grant	Expiry Date	Vest Terms
Joanne Beck	FMV Options*	26 June 2019	35,000	$13.20	$462	$287	25 June 2029	(1)
Marc Dunoyer	FMV Options*	26 June 2019	35,000	$13.20	$462	$287	25 June 2029	(1)
James Geraghty	FMV Options*	26 June 2019	35,000	$13.20	$462	$287	25 June 2029	(1)
Charles Rowland	FMV Options*	26 June 2019	35,000	$13.20	$462	$287	25 June 2029	(1)
Alicia Secor	FMV Options*	26 June 2019	35,000	$13.20	$462	$287	25 June 2029	(1)
Jon Ellis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
John Curnutte	FMV Options*	30 August 2019	50,000	$14.80	$740	$449	29 August 2029	(2)

* The fair market value options are granted at the market price which is the exercise price. The face value at date of grant is calculated as the number of shares multiplied by the exercise price. The fair value at date of grant is calculated as the Black Scholes value.

(1) The options vest, and become exercisable at the earlier of one year from the date of grant or the next AGM.

(2) The options vest, and become exercisable, over a three-year period on a monthly basis commencing upon the one-month anniversary of the grant date.

Jon Ellis received no option grants during the year.

Payments to former Directors (audited)

No payments were made to former Directors of the Company during the year.

External directorships

The Executive Directors do not currently hold any outside directorships.

Statement of Directors' shareholding and share interests (audited)

The share interests of each Director as at 31 December 2020 (together with interests held by his or her connected persons) are set out in the table below.

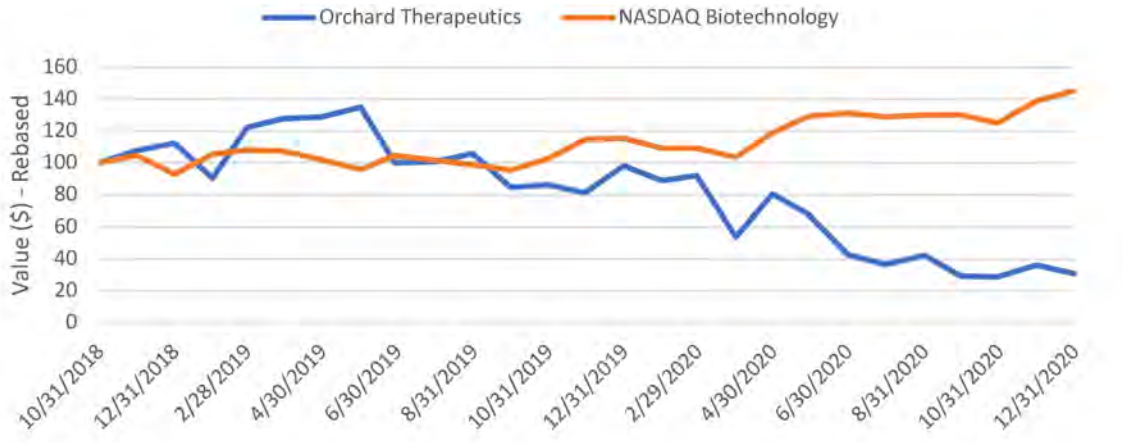
Orchard Therapeutics does not operate any formal shareholding guidelines for Directors' shareholding requirements.

		Shares		Share Options		
	Beneficially owned shares as at 31/12/20[1]	Unvested without performance conditions	Unvested with performance conditions	Vested but unexercised	Unvested without performance conditions	Unvested with performance conditions
Executive Directors						
Mark Rothera	103,796	–	–	1,548,808	–	–
Bobby Gaspar	355,158	–	18,750[2]	800,238	484,064	–
Non-Executive Directors						
Joanne Beck	9,294	–	–	101,624	48,406	–
John Curnutte	–	–	–	22,083	62,917	–
Marc Dunoyer	37,179	–	–	101,625	48,405	–
Jon Ellis	–	–	–	–	–	–
James Geraghty	44,391	–	–	319,373	70,747	–
Charles Rowland	12,294	–	–	101,625	48,405	–
Alicia Secor	–	–	–	68,250	51,750	–
Steven Altschuler	–	–	–	13,888	71,112	–

1. Mr Rothera's ownership reflects his beneficial ownership at date of termination March 17, 2020.
2. 6,250 shares vested on 8 January 2021 following completion of the performance milestone relating to Libmeldy's approval by the European Commission.

Performance graph and table

The chart below shows the Company's Total Shareholder Return (TSR) performance compared with that of the NASDAQ Biotechnology Index over the period from the date of the Company's admission to 31 December 2020. The NASDAQ Biotechnology Index has been chosen as an appropriate comparator as it is the index of which the Company is a constituent. TSR is defined as the return on investment obtained from holding a company's shares over a period. It includes dividends paid, the change in the capital value of the shares and any other payments made to or by shareholders within the period.



This graph shows the value, by 31 December 2020, of $100 invested in Orchard Therapeutics on 31 October 2018 at the IPO price of $14, compared with the value of $100 invested in the NASDAQ Biotechnology Index.

Aligning pay with performance

The total remuneration figure for the CEO is shown in the table below, along with the value of bonuses paid, and SOIP vesting, as a percentage of the maximum opportunity:

Chief Executive Officer	**2018**	**2019**	**2020**
Total remuneration ($000)[1]	$555	$1,016	$764
Actual bonus (% of the maximum)	N/A	44%*	37.5%*
SOIP vesting (% of the maximum) **	N/A	N/A	N/A

1 For 2018 and 2019, these figures are for Mr. Rothera and for 2020 the full-year remuneration for Dr. Gaspar.

* Calculated as the bonus earned in the in year by Dr Gaspar (60% of salary) expressed as a portion of the maximum available under the Company's Directors' Remuneration Policy 160% of salary

** There is no maximum grant policy under the SOIP; therefore, this information cannot be disclosed.

Relative importance of spend on pay

The table below illustrates the Company's expenditure on pay by the Group in comparison to research and development expenses. R&D expenses have been chosen as an appropriate measure of the Company's major year-on-year expenditure.

	2019	2020	% change
Research and development expenses	$117,363	$97,730	-20.1%
Total employee pay expenditure ($'000)[1]	$69,486	$87,091	25.3%

1. Total employee pay expenditure in the table above is inclusive of cash payments for salaries and wages, as well as employer benefits and tax costs. It also includes $27,962k and $19,424k in non-cash share-based compensation expense for 2020 and 2019 respectively.

Average percentage change in remuneration of Directors and Employees

As required by the 2019 regulations, the table below shows a comparison of the annual change of each individual director's pay to the annual change in average employee pay in the year ended 31 December 2020.

	Base salary/fee change	Bonus change[1]	Benefit change[1]
Executive Directors			
Bobby Gaspar	57.7%	-54%	0%
Non-Executive Directors			
Joanne Beck	41.4%	n/a	n/a
John Curnutte[2]	278%	n/a	n/a
Marc Dunoyer	26.5%	n/a	n/a
Jon Ellis[3]	n/a	n/a	n/a
James Geraghty	15%	n/a	n/a
Charles Rowland	31.1%	n/a	n/a
Alicia Secor	23%	n/a	n/a
Steven Altschuler[4]	n/a	n/a	n/a
Average employee[5]	n/a	n/a	n/a

1 None of the Non-Executive Directors are eligible for an annual bonus and none claimed any benefits during the year.
2 John Curnutte joined the Board in 2019 and the remuneration received in 2019 was not a full annual amount.
3 Jon Ellis does not receive any remuneration for his services to the Board
4 Steven Altschuler joined the Board during 2020 and therefore no comparative information is shown.
5 As the parent company Orchard Therapeutics Plc has no direct employees. All employees are employed by the relevant local entities.

Statement of implementation of remuneration policy in 2021

Annual base salary

	Base salary 2020	Base salary 2021	% change
Bobby Gaspar, Chief Executive Officer,	£440,000	£440,000	0%

Benefits and pension

In 2020, Executive Directors are eligible for the same benefits (such as health insurance and pension) as provided to all employees in the jurisdiction in which they reside. Pension contributions for Executive Directors are up to 6% of base salary which may be taken as a cash allowance. 6% is the rate provided to all employees in the UK and therefore representative of the workforce rate.

Annual Bonus

The CEO will be entitled to a target bonus of 60% of base salary, with the maximum payout up to 150% of target bonus (90% salary).

Following the Compensation Committee's decision to only pay 50% of the 2020 annual bonus in cash, an additional award of 55,006 options was made on 1 February 2021. These options vest on a monthly basis over 12 months from the date of grant.

These 2021 targets and maximum have been set within the overall Directors' Remuneration Policy. Unless otherwise determined by the Compensation Committee, the bonus will be paid in cash and subject to the achievement of a number of strategic objectives determined by the Committee.

Specific targets are commercially sensitive and therefore are not disclosed in advance. However, full details of the targets and performance against them will be disclosed when they are no longer considered commercially sensitive.

Share Option Incentive Plan (SOIP)

Annual award of share options

In February 2021 as part of the annual compensation package, the CEO was granted 850,000 share options in the Company at an exercise price of $5.98, based on the closing price of the Company's ADSs on the Nasdaq Global Select Market on 1 February 2021.

Following the Compensation Committee's decision to only pay 50% of the annual bonus in cash, an additional award of 55,006 options was made on 1 February 2021.

Executive Director	Form of Award	Date of Grant	Shares Covered	Exercise Price	Face Value	Fair Value (Black-Scholes)	Expiry Date	Vest Terms
Bobby Gaspar	FMV Options*(1)	01 February 2021	850,000	$5.98	$5,083,000	$3,241,354	31 Jan 2031	(1)
Bobby Gaspar	FMV Options*(2)	01 February 2021	55,006	$5.98	$329,474	$209,758	31 Jan 2031	(2)

(1) The share options will expire 10 years from the date of grant. The share options vest monthly over a 4-year period and are subject to any further performance conditions.
(2) These awards will vest monthly over 12 months from the 1 February 2021.

At the date of this report, there is no intention to make any further awards under the SOIP to any Directors. Any awards made during the year will be disclosed in the relevant Directors' Remuneration Report.

Non-Executive Directors' fees for 2021

Non-Executive Directors are eligible to receive the following cash compensation annually:

	2021 Fee in $'000	2020 Fee in $'000
Base fee:		
Board Chair	$85	$85
Board Member	$45	$45
Additional fees:		
Audit Committee Chair	$18	$18
Audit Committee Member	$9	$9
Compensation Committee Chair	$15	$15
Compensation Committee Member	$7.5	$7.5
Nominating and Corporate Governance Committee Chair	$10	$10
Nominating and Corporate Governance Committee Member	$5	$5
Science and Technology Committee Chair	$10	$10
Science and Technology Committee Member	$7.5[1]	$5

1. The increase in the Science and Technology Committee fee is effective 1 April 2021.

The Company provides an initial, one-time equity award of 57,500 stock options to each new Non-Executive Director upon his or her election to our board of directors. Under normal circumstances, initial share awards vest monthly over three years. The Company intends to provide an annual equity incentive award of 40,000 stock options to each Non-Executive Director at the AGM. Options awarded annually will usually vest upon the earlier to occur of the first anniversary of the date of grant or the date of the next annual general meeting.

Non-Executive Directors will not be eligible to participate in any performance-based incentive plans.

Jon Ellis does not receive fees for his services on the Board.

Each Non-Executive Director will also be entitled to reimbursement of reasonable expenses and reimbursement of up to $2,500 for tax preparation assistance if Board services requires a Non-Executive Director to file a tax return in a jurisdiction that the director otherwise would not have been required to file.

On behalf of the Board
Charles Rowland, Jr.
Chair of the Compensation Committee

9 April 2021

ORCHARD THERAPEUTICS PLC
PARENT COMPANY FINANCIAL STATEMENTS
FOR THE YEAR ENDED 31 December 2020

Registered Number: 11494381

Parent Company Balance Sheet

for the year ended 31 December 2020

	NOTE	2020 $'000	2019 $'000
NON-CURRENT ASSETS			
Investment	2	279,625	844,904
CURRENT ASSETS			
Debtors	3	36,528	122,283
Prepaid expenses and other deferred costs	4	3,862	308
Marketable securities at fair value through other comprehensive income	5	119,414	234,596
Cash and cash equivalents		15,196	9,365
CURRENT LIABILITIES			
Creditors – amounts falling due within one year	6	(5,727)	(1,837)
NET CURRENT ASSETS		169,273	364,715
TOTAL ASSETS LESS CURRENT LIABILITIES		448,898	1,209,619
Creditors – amounts falling due after more than one year	7	(20,204)	(24,699)
NET ASSETS		428,694	1,184,920
CAPITAL AND RESERVES			
Called up share capital	8	12,497	12,321
Share premium		339,435	334,706
Share compensation reserve		115,062	74,233
Other comprehensive income		83	218
(Accumulated losses)/Retained earnings		(38,383)	763,442
TOTAL EQUITY		428,694	1,184,920

The above parent company balance sheet should be read in conjunction with the accompanying notes.

The company has elected to take the exemption under section 408 of the Companies Act of 2006 from presenting the company statement of comprehensive income. The company loss for the year ended 31 December 2020 was a loss of $801.8 million (2019: loss of $2.9 million).

The parent company financial statements on pages 121-130 were approved by the Board of Directors on 9 April 2021 and were signed on its behalf by:

Bobby Gaspar
Director
9 April 2021
Registered number: 11494381

Parent Company Statement of Changes in Equity

for the year ended 31 December 2020

	Shares Number	Called Up Share Capital $'000	Share Premium $'000	Share Compensation Reserve $'000	Other Comprehensive Income $'000	(Accumulated losses)/ Retained Earnings $'000	Total $'000
At 1 January 2019	85,865,557	10,914	203,140	34,943	–	766,360	1,015,357
Follow-on offering proceeds	9,725,268	1,233	129,036	–	–	–	130,269
Underwriter and issuance costs	–	–	(605)	–	–	–	(605)
Issue of shares under employee equity plans	1,332,904	174	3,135	–	–	–	3,309
Share-based compensation	–	–	–	39,290	–	–	39,290
Unrealized gain on marketable securities	–	–	–	–	218	–	218
Loss for the year	–	–	–	–	–	(2,918)	(2,918)
Balance at 31 December 2019	96,923,729	12,321	334,706	74,233	218	763,442	1,184,920
Issue of shares under employee equity plans	1,261,703	163	3,951	–	–	–	4,114
Issuance of shares under license agreements	98,171	13	778	–	–	–	791
Share-based compensation	–	–	–	40,829	–	–	40,829
Unrealized loss on marketable securities	–	–	–	–	(135)	–	(135)
Loss for the year	–	–	–	–	–	(801,825)	(801,825)
Balance at 31 December 2020	98,283,603	12,497	339,435	115,062	83	(38,383)	428,694

The above parent company statement of changes in equity should be read in conjunction with the accompanying notes.

1. COMPANY ACCOUNTING POLICIES

BASIS OF PRESENTATION AND ACCOUNTING PRINCIPLES

Orchard Therapeutics plc (the "Company") and its subsidiaries (the "Group" or "Orchard") is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. The Groups's ex vivo autologous gene therapy approach utilizes genetically-modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Group is advancing seven clinical-stage programs across multiple therapeutic areas, including inherited neurometabolic disorders, primary immune deficiencies and blood disorders, 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 limited by shares, incorporated pursuant to the laws of England and Wales. Our registered office is located at 108 Cannon Street, London, EC4N 6EU, United Kingdom. Orchard Therapeutics plc was originally incorporated under the laws of England and Wales in August 2018 to become a holding company for Orchard Therapeutics (Europe) Limited.

The financial statements have been prepared in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 102 "The Financial Reporting Standard applicable in the UK and Republic of Ireland" and applicable law) and the Companies Act 2006. The financial statements are prepared under the historical cost convention.

The Company is included in the Group financial statements of Orchard Therapeutics plc, which are included within this Annual Report.

The principal accounting policies applied in the preparation of these financial statements are set out below. These policies have been consistently applied to all the years presented, unless otherwise stated. The Company has adopted FRS 102 in these financial statements. The Company has taken advantage of the following disclosure exemptions in preparing these financial statements, as permitted by FRS 102: "The Financial Reporting Standard applicable in the UK and Republic of Ireland."

- the requirements of Section 7 Statement of Cash Flows;
- the requirements of Section 3 Financial Statement Presentation paragraph 3.17(d);
- the requirements of Section 11 Financial Instruments paragraphs 11.42, 11.44, 11.45, 11.47, 11.48(a)(iii), 11.48(a)(iv), 11.48(b) and 11.48(c);
- the requirements of Section 33 Related Party Disclosures paragraph 33.7;
- the requirements of Section 26 Share-based Payments paragraphs 26.18(b), 26.19-26.21 and 26.23

The Company has chosen to adopt Sections 11 and 12 of FRS 102 in respect of financial instruments.

The financial statements and related notes have been prepared and presented in U.S. Dollars. Unless otherwise noted, amounts are presented in USD thousands.

INVESTMENTS

The investment in the subsidiary arose on the reorganization of the Group in 2018. The investment is recorded at cost less accumulated impairment losses. The cost is based on the directors' estimated fair value of Orchard Therapeutics (Europe) Limited having regard to the valuations that were available prior to the IPO in November 2018, additions to the investment associated with the value of share-based payment charges associated with subsidiary employees, and conversion of intercompany debts to equity investments. Where at the year-end there is evidence of impairment, the carrying value of the investment is written down to its recoverable amount.

FOREIGN CURRENCY

Foreign currency transactions are translated into the functional currency using the spot exchange rates at the dates of the transactions. At each period end foreign currency monetary items are translated using the closing rate. Non-monetary items measured at historical cost are translated using the exchange rate at the date of the transaction and non-monetary items measured at fair value are measured using the exchange rate when fair value was determined.

GOING CONCERN

The financial statements have been prepared on a going concern basis. The Directors have considered the appropriateness of the going concern basis in the Directors' Report. In addition, the Parent Company acknowledges its responsibility to support its subsidiaries' cash outflows for the foreseeable future. At 31 December 2020 the Group held cash, cash equivalents, and marketable securities of $191.9 million, and the Parent Company held cash, cash equivalents, and marketable securities of $134.6 million. The directors have prepared a forecast through 2022 and expect that cash, cash equivalents, and marketable securities on hand as of December 31, 2020, together with the proceeds from the Private Placement of $150.0 million of ordinary shares that closed in February 2021 (see Note 11, Subsequent Events), will be sufficient to fund operations and capital expenditure requirements for at least 12 months from the issuance of these financial statements. The directors have considered the effect of the COVID-19 pandemic on our forecast, and have determined it does not have an effect on our ability to operate as a going concern for at least 12 months from the issuance of these financial statements. Therefore, the directors have at the time of approving the financial statements, a reasonable expectation that the Group and Company have adequate resources to continue in operational existence for the foreseeable future and for a period of at least 12 months from the date of signing these financial statements. Accordingly, the Group and Company continues to adopt the going concern basis of accounting in preparing these financial statements.

SHARE-BASED PAYMENTS

The financial effect of awards by the Parent Company of options and other equity-based awards over its equity shares to the employees of subsidiary undertakings are recognized by the Parent Company in its individual financial statements. In particular, the Parent Company records a capital contribution to the subsidiary with a corresponding credit to the share compensation reserve. The expense associated with the equity-based awards is recognized in profit and loss for the subsidiary undertaking, and a corresponding capital contribution from the Parent Company in the subsidiary's equity. The expense associated with equity-based awards to our Non-executive Directors is recognized in profit and loss for the Parent Company.

The Parent Company recognizes the capital contribution associated with the share-based compensation expense for awards granted to employees a straight-line basis over the requisite service period. The fair value of each share option is estimated on the grant date using the Black Scholes option pricing model.

CASH AND CASH EQUIVALENTS

Cash and cash equivalents include cash in hand, deposits held at call with banks, and other short-term highly liquid investments with original maturities of three months or less.

DEBTORS

Debtors are amounts due from other group companies for services performed in the ordinary course of business. Debtors are recognised initially at fair value and subsequently measured at amortised cost using the effective interest method, less provision for impairment.

MARKETABLE SECURITIES AT FAIR VALUE THROUGH OTHER COMPREHENSIVE INCOME

Marketable securities consist of debt securities with original maturities of greater than ninety days. 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).

CREDITORS – AMOUNTS FALLING DUE WITHIN ONE YEAR

Trade creditors are obligations to pay for goods or services that have been acquired in the ordinary course of business from suppliers. Trade creditors are recognised initially at fair value and subsequently measured at amortised cost using the effective interest method.

CREDITORS – AMOUNTS FALLING DUE AFTER MORE THAN ONE YEAR

Creditors for amounts falling due after more than one year are notes payable, which are carried at amortised cost, using the effective interest method. Issuance costs paid to establish our notes payable are recognized as on offset to the associated notes payable and amortised as interest expense over the term of the loan. To the extent that portions of our term loan facility are not drawn down, the issuance costs are deferred until the draw-down occurs.

SHARE CAPITAL

Ordinary shares are classified as equity. Incremental costs directly attributable to the issuance of share capital are shown as a deduction to equity, net of tax.

CRITICAL ACCOUNTING ESTIMATES AND JUDGMENTS

The preparation of financial statements in conformity with FRS102 requires the use of accounting estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements. Although these estimates are based on management's best knowledge of current events and actions, actual results ultimately may differ from those estimates. FRS102 requires management to exercise judgment in the process of applying the accounting policies.

Investment in subsidiary

Management perform an annual impairment assessment of the investment held in Orchard Therapeutics (Europe) Limited by the Company. The valuation of the subsidiary is derived from publicly available information, being the market capitalisation of the group, as at the year end date, given that the future value of the group is expected to be generated from the products and treatments which are being developed by the subsidiary companies. On the balance sheet date, where the market capitalisation of the group as a whole falls below the carrying value of the investment, management will perform a fair value less cost to sell calculation and then consider whether an impairment of the investment is required, and if so, will write down the cost of the investment to its recoverable amount, with an associated impairment charge recognised in the parent company profit and loss account. In the event the Group's market capitalisation increases and the reasons for any impairment loss have ceased to apply, an impairment loss may be reversed in a subsequent period in the Parent Company profit and loss account, to the extent the carrying value would have been determined had no impairment loss been recognized for the investment in prior years.

2. INVESTMENTS

	Subsidiary undertakings ($000)
As at 1 January 2020	**844,904**
Share-based payments associated with subsidiary employees	36,959
Intercompany capitalisation	190,610
Provision for impairment	(792,846)
As at 31 December 2020	**279,625**

	Subsidiary undertakings ($000)
Cost and net book value	**1,072,473**
Accumulated provision for impairment	(792,625)
As at 31 December 2020	**279,625**

Share-based payment cost of $37.0 million in 2020 was recorded as a capital contribution from Orchard Therapeutics plc to Orchard Therapeutics (Europe) Limited and subsidiaries, as a capital injection in the Company's Balance Sheet.

On 23 July 2020 and 10 December 2020, the Company received 100,000 and 30,000 £0.00001 ordinary shares respectively in Orchard Therapeutics (Europe) Limited in exchange for a total of $190.6 million of intercompany debt due to the Company.

The Parent Company performed an impairment analysis on a fair value less cost to sell basis, whereby the Parent Company used the market capitalisation of the Group as the approximate fair value and the cost to sell and control premium were deemed to be negligible. The carrying value of the investment exceeded the fair value less cost to sell of the investment as at 31 December 2020, and the Parent Company concluded that the investment was impaired by $792.8 million (2019: $nil). If the market capitalisation of the group increases subsequent to the year end, then all or a portion of this impairment charge could be reversed in future years.

SUBSIDIARY UNDERTAKINGS

Name of undertaking	Class of shareholding	Proportion held	Nature of business
Orchard Therapeutics (Europe) Limited	Ordinary	100%*	Research and development
Orchard Therapeutics North America	Ordinary	100%	Research and development
Orchard Therapeutics (Netherlands) B.V.	Ordinary	100%	Selling, general, and administrative
Orchard Therapeutics (France) SAS	Ordinary	100%	Selling, general, and administrative
Orchard Therapeutics (Italy) S.r.l	Ordinary	100%	Selling, general, and administrative
Orchard Therapeutics (Germany) GmbH	Ordinary	100%	Selling, general, and administrative

*Held directly by Orchard Therapeutics plc

Orchard Therapeutics North America and Orchard Therapeutics (Netherlands) B.V. are subsidiary undertakings of Orchard Therapeutics (Europe) Limited. Orchard Therapeutics (France) SAS, Orchard Therapeutics (Italy) S.r.l. and Orchard Therapeutics (Germany) GmbH are subsidiary undertakings of Orchard Therapeutics (Netherlands) B.V.. The following table outlines the country of incorporation and registered office of each of the subsidiary undertakings:

Name of undertaking	Country of incorporation	Registered office
Orchard Therapeutics (Europe) Limited	United Kingdom	108 Cannon Street, London, EC4N 6EU, United Kingdom
Orchard Therapeutics North America	United States	101 Seaport Blvd., Boston, MA 02210, United States
Orchard Therapeutics (Netherlands) B.V.	Netherlands	Prins Berhardplein 200, 1097 JB, Amsterdam, Netherlands
Orchard Therapeutics (France) SAS	France	23 rue du Roule 75001, Paris, France
Orchard Therapeutics (Italy) S.r.l	Italy	Milano (MI) Largo Guido, Donegani 2 Cap 20121, Italy
Orchard Therapeutics (Germany) GmbH	Germany	TRIBES Dusseldorf GAP, Graf-Adolf-Platz 15, 40213 Dusseldorf, Germany

3. DEBTORS

	2020 $000	2019 $000
Amounts owed by subsidiary undertakings	35,415	119,679
Other receivables	1,113	2,604
	36,528	**122,283**

Amounts owed by subsidiary undertakings are unsecured, interest free, have no fixed date of repayment and are repayable on demand.

4. PREPAID EXPENSES AND OTHER DEFERRED COSTS

	2020 $000	2019 $000
Deferred financing costs	975	307
Prepaid expenses	2,887	1
	3,862	**308**

5. MARKETABLE SECURITIES AT FAIR VALUE THROUGH OTHER COMPREHENSIVE INCOME

	2020 $000	2019 $000
Marketable debt securities	119,414	234,596
	119,414	**234,596**

6. CREDITORS

– Amounts falling due within one year

	2020 $000	2019 $000
Bank loans and overdrafts	4,861	–
Trade creditors	270	323
Accruals	596	1,514
	5,727	**1,837**

7. CREDITORS – amounts falling due after more than one year

In May 2019, as amended in April 2020, the Company entered into a senior term facilities agreement (the "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 $25 million increments. To date, the Company has borrowed $25.0 million under an initial term loan. The remaining $50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan at the Company's discretion and upon achievement of certain regulatory milestones and maintenance of $100 million and $125 million in cash and cash equivalent investments, respectively. The second term loan of $25.0 million is available between 1 July 2020 and 31 March 2021. The third term loan of $25.0 million is available between 1 July 2020 and 30 September 2021. As of 31 December 2020, the Company had met the criteria to draw down the second and third term loans totaling $50.0 million, but these have not been drawn down as at 31 December 2020.

The term loans under the Credit Facility will terminate in May 2024. Each term loan under the Credit Facility bears interest at an annual rate equal to 6% plus LIBOR. The Company is required to make interest-only payments on the term loan for all payment dates prior to 24 months following the date of the Credit Facility, unless the third tranche is drawn, in which case the Company is required to make interest-only payments for all payment dates prior to 36 months following the date of the Credit Facility. The term loans under the Credit Facility will begin amortizing on either the 24-month or the 36-month anniversary of the 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 4.5% is due upon termination. The Company accrues the final payment amount of $1.1 million associated with the first term loan, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the maturity date.

As of 31 December 2020 and 2019, bank loans consist of the following:

	2020 $000	2019 $000
Notes payable, net of unamortized debt issuance costs	24,659	24,541
Less: current portion	(4,861)	–
Notes payable, net of current portion	**19,798**	**24,541**
Accretion related to final payment	406	158
Bank loans and overdrafts, long term	**20,204**	**24,699**

As of 31 December 2020, estimated future principal payments due are as follows:

	Aggregate Minimum Payments $000
Total principal payments due	25,000
Final payment	1,125
Total payments	**26,125**
Less: current portion	(4,861)
Less: unamortized portion of final payment	(719)
Less: unamortized debt issuance costs	(341)
Bank loans and overdrafts, long term	**20,204**

Interest expense for the year ended 31 December 2020 was $2.3 million (2019: $1.5 million).

8. CALLED UP SHARE CAPITAL

	2020 $000	2019 $000
Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 shares	12,497	12,321
	12,497	**12,321**

As of 31 December 2020 and 2019, the Company had authority to allot ordinary shares up to a maximum nominal value of £13,023,851.50 with a nominal value of £0.10 per share. As of 31 December 2020 and 2019, there were 98,283,603 and 96,923,729 ordinary shares issued and outstanding, respectively. As of 31 December 2020 and 2019, there were a total of 13,895,643 and 12,216,140 share options in respect of ordinary shares outstanding, respectively. In addition, as of 31 December 2020 and 2019, there were 644,000 and 556,422 unvested restricted share units outstanding in respect of ordinary shares outstanding, respectively.

In April 2020, the Company issued 75,413 ordinary shares to Oxford BioMedica pursuant to the terms of a license agreement with our subsidiary.

In December 2020, the Company issued 22,758 ordinary shares pursuant to a consulting agreement with a non-employee advisor with our subsidiary.

During the year ended 31 December 2020, the Company issued 1,154,441 shares as a result of share option exercises, and 107,262 shares from our employee share purchase plan.

As of 31 December 2020 and 2019, each holder of ordinary shares is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. As of 31 December 2020, the Company has not declared any dividends (2019: $nil).

Share premium represents the excess paid for the issuance of ordinary shares, over and above their nominal value.

The share based compensation reserve exists due to the share options issued by the company to its employees within the group.

9. RELATED PARTY TRANSACTIONS

These are disclosed as part of note 18 in the consolidated financial statements. The Company has taken advantage of the exemption, under FRS 102 'The Financial Reporting Standard applicable in the UK and Republic of Ireland', not to disclose related party transactions with other companies that are wholly owned within the group.

10. ULTIMATE PARENT UNDERTAKING AND CONTROLLING PARTY

There is no ultimate parent undertaking or controlling party of the Company as ownership is split between the Company's shareholders.

11. SUBSEQUENT EVENTS

Securities Purchase Agreement

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 (the "Private Placement"). The Private Placement resulted in net proceeds to the Company of approximately $144.0 million after deducting placement agent fees. 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.

ORCHARD THERAPEUTICS PLC
CONSOLIDATED FINANCIAL STATEMENTS
FOR THE YEAR ENDED 31 December 2020

Registered Number: 11494381

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

	December 31,	
	2020	2019
Assets		
Current assets:		
Cash and cash equivalents	$ 55,135	$ 19,053
Marketable securities	136,813	305,937
Trade receivables	878	1,442
Prepaid expenses and other current assets	13,365	8,530
Research and development tax credit receivable	17,344	14,934
Total current assets	223,535	349,896
Non-current assets:		
Operating lease right-of-use-assets	29,815	19,415
Property and equipment, net	4,781	7,596
Research and development tax credit receivable, net of current portion	—	13,710
Restricted cash	4,266	4,264
Other assets	18,540	4,400
Total non-current assets	57,402	49,385
Total assets	$ 280,937	$ 399,281
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 8,823	$ 11,984
Accrued expenses and other current liabilities	28,943	37,980
Operating lease liabilities	8,934	5,892
Notes payable, current	4,861	—
Total current liabilities	51,561	55,856
Notes payable, long-term	20,204	24,699
Operating lease liabilities, net of current portion	24,168	15,320
Other long-term liabilities	6,570	4,213
Total liabilities	102,503	100,088
Commitments and contingencies (Note 16)		
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, 2020 and 2019, respectively; 98,283,603 and 96,923,729 shares issued and outstanding at December 31, 2020 and 2019, respectively.	12,507	12,331
Additional paid-in capital	771,194	738,481
Accumulated other comprehensive income	373	2,042
Accumulated deficit	(605,640)	(453,661)
Total shareholders' equity	178,434	299,193
Total liabilities and shareholders' equity	$ 280,937	$ 399,281

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,	
	2020	2019
Product sales, net	$ 2,595	$ 2,513
Costs and operating expenses		
Cost of product sales	857	805
Research and development	93,730	117,363
Selling, general and administrative	64,986	57,218
Total costs and operating expenses	159,573	175,386
Loss from operations	(156,978)	(172,873)
Other income (expense):		
Interest income	3,185	7,362
Interest expense	(2,328)	(1,538)
Other income, net	3,411	1,387
Total other income (expense), net	4,268	7,211
Net loss before income tax	(152,710)	(165,662)
Income tax benefit	731	2,240
Net loss attributable to ordinary shareholders	$ (151,979)	$ (163,422)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.53)	$ (1.75)
Weighted average number of ordinary shares outstanding, basic and diluted	99,445,874	93,240,355
Other comprehensive (loss) income		
Foreign currency translation adjustment	(1,485)	(1,387)
Unrealized gain (loss) on marketable debt securities	(184)	266
Total other comprehensive loss	(1,669)	(1,121)
Total comprehensive loss	$ (153,648)	$ (164,543)

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, 2018	**85,865,557**	**$ 10,924**	**$ 587,490**	**$ 3,163**	**$ (290,239)**	**$ 311,338**
Share-based compensation expense	—	—	19,424	—	—	19,424
Exercise of share options	1,209,335	158	1,845	—	—	2,003
Issuance of ESPP shares	123,569	16	1,290	—	—	1,306
Issuance of ADSs in follow-on offering, net of issuance costs of $605	9,725,268	1,233	128,432	—	—	129,665
Foreign currency translation	—	—	—	(1,387)	—	(1,387)
Unrealized gain on marketable debt securities	—	—	—	266	—	266
Net loss	—	—	—	—	(163,422)	(163,422)
Balance at December 31, 2019	**96,923,729**	**$ 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 license agreements	98,171	13	778	—	—	791
Foreign currency translation	—	—	—	(1,485)	—	(1,485)
Unrealized loss 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**

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

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

	Year Ended December 31,	
	2020	2019
Cash flows from operating activities		
Net loss attributable to ordinary shareholders	$ (151,979)	$ (163,422)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	2,004	1,675
Share-based compensation	27,962	19,424
Impairment of long-lived assets	5,650	—
Non-cash interest expense	500	311
Amortization of provision on loss contract	(2,413)	(3,855)
Non-cash consideration for licenses and milestones	791	—
Deferred income taxes	(2,257)	(2,942)
Amortization of (discount) premium on marketable securities	770	(676)
Unrealized foreign currency and other non-cash adjustments	(3,674)	(1,859)
Changes in operating assets and liabilities:		
Trade receivables	582	715
Research and development tax credit receivable	11,674	(17,564)
Prepaids and other assets	(5,070)	(2,209)
Operating leases, right-of-use-assets	5,863	3,064
Accounts payable	(1,553)	(6,413)
Accrued expenses and other current liabilities	(10,725)	11,434
Other long-term liabilities	2,570	(1,424)
Operating lease liabilities	(6,969)	(2,390)
Net cash used in operating activities	$ (126,274)	$ (166,131)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	281,433	109,019
Purchases of marketable securities	(113,262)	(414,010)
Payment of construction deposit	(10,000)	—
Receipt of funds from construction deposit	1,876	—
Purchases of property and equipment	(2,668)	(4,367)
Net cash used in investing activities	$ 157,379	$ (309,358)
Cash flows from financing activities		
Issuance of debt from credit facility, net of issuance costs	—	24,466
Issuance of ADRs in public offerings	—	130,270
Payment of offering costs	—	(605)
Proceeds from employee equity plans	3,936	3,322
Net cash provided by financing activities	$ 3,936	$ 157,453
Effect of exchange rate changes on cash	1,043	1,672
Net increase (decrease) in cash and restricted cash	$ 36,084	$ (316,364)
Cash, cash equivalents, and restricted cash —beginning of year	23,317	339,681
Cash, cash equivalents, and restricted cash —end of year	$ 59,401	$ 23,317
Supplemental disclosure of non-cash investing and financing activities		
Intangible assets and property and equipment in accounts payable and accrued expenses	3,096	647
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	17,486	—
Cash paid for interest	1,828	1,227
Cash paid for taxes	1,007	1,474

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 rare 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 full, or standard, marketing authorization from the European Commission for Libmeldy™ (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 metchromatic 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.

The Company 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 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, 2020, 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 $152.0 million and $163.4 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, the Company had an accumulated deficit of $605.6 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, 2020 of $191.9 million, together with the proceeds from the Private Placement of $150.0 million of ordinary shares that closed in February 2021 (see Note 20), 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.

Deferred income taxes in the consolidated statement of cash flows for the year-ended December 31, 2019 previously included in changes in prepaid expenses and other assets has been presented as a separate line item as a non-cash item within adjustments to reconcile net loss to net cash used in operating activities in the consolidated statement of cash flows to conform to current period presentation.

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

UK Companies Act 2006 additional disclosures

Additional disclosures required for the group financial statements under the Companies Act 2006 are shown on page 3 of the Annual Report and in the auditable part of the Directors' Remuneration Report on pages 109-115.

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, operating lease assets and liabilities, and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. The future developments of the COVID-19 pandemic also may directly or indirectly impact the Company's business include quarantines, border closures, increased border controls, travel restrictions, shelter-in-place orders and shutdowns, business closures, cancellations of public gatherings and other measures. 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 stockholders' 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 gains of $3.4 million, and $1.4 million for the years ended December 31, 2020 and 2019, 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 $3.7 million and $1.1 million located in the United Kingdom and United States, respectively, as of December 31, 2020. The Company had property and equipment of $2.6 million and $5.0 million located in the United Kingdom and United States, respectively, as of December 31, 2019. 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. The Company had right-of-use assets in the United States and United Kingdom and European Union of $15.7 million and $3.7 million, respectively, as of December 31, 2019.

Cash and 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, and is limited to the amount by which fair value is less than amortized cost. The credit-related impairment amount is recognized in net income; 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

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, 2020 and 2019. 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, 2020 and 2019.

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,	
	2020	2019
Cash and cash equivalents	$ 55,135	$ 19,053
Restricted cash	4,266	4,264
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 59,401	$ 23,317

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 statement 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, 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. Actual results could differ from the estimates made by the Company. The historical accrual estimates made by the Company have not been materially different from the actual costs.

Share-based compensation

The Company measures all stock options and other stock-based awards granted to employees at fair value on the date of grant. The Company uses the Black-Scholes option-pricing model in the valuation of its stock options. The fair value of performance-based share awards and restricted stock units is based on the fair value of the stock on the date of grant. The Company uses the Monte-Carlo model in order to calculate the fair value of the market-based awards. The fair value of options is recognized as stock-based compensation expense over the requisite service period, which is generally the vesting period of the respective award. The Company accounts for stock-based compensation expense related to forfeitures as the forfeitures occur. The straight-line method of expense recognition is applied to all awards with service-based and market-based conditions. The Company records stock-based compensation expense related to performance-based awards when the performance-based targets are probable of being achieved. The Company classifies stock-based compensation expense in the consolidated statements of operations in the same manner in which the award recipient's payroll costs are classified.

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 debt securities and foreign currency translation.

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 practical expedients are available to entities. Entities electing the practical expedient 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 practical expedient and 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 (Note 13). 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 as part of the GSK transaction 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 Strimvelis and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a credit to research and development expense. We have made an estimate of the expected future losses associated with Strimvelis and adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. 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 updates to estimates of potential future losses. The Company paused treating new patients with Strimvelis in October 2020 upon learning that a patient treated with the drug in 2016 under a compassionate use program was diagnosed with lymphoid T cell leukemia, a known risk factor for gammaretroviral vector-based gene therapy. The EMA's Committee for Medicinal Products for Human Use, or CHMP, reviewed the updated risk-benefit assessment of Strimvelis as part of its ongoing MAA renewal procedure, concluded that the risk-benefit balance remains favorable and recommended in February 2021 that the marketing authorization for Strimvelis be renewed for five years, allowing marketing of Strimvelis to resume. The Company will continue to evaluate its future estimates for amortization of the Strimvelis loss provision. The following table below outlines the changes to the Strimvelis loss provision for the periods ended December 31, 2020 and 2019:

	Year Ended December 31,	
	2020	2019
Balance at beginning of period	$ 6,790	$ 10,339
Provisions	—	—
Amortization of loss provision	(2,413)	(3,855)
Foreign currency translation	105	306
Balance at end of period	$ 4,482	$ 6,790

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. As of December 31, 2019, $3.0 million of the Strimvelis loss provision was classified as current, and $3.8 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 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 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 carried 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, 2020. The Company has qualified under the more favorable SME regime for the year ended December 31, 2019 and expects to qualify under the SME regime for the year ending December 31, 2020.

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, 2020 and 2019:

	Year Ended December 31,	
	2020	2019
Balance at beginning of period	$ 28,644	$ 10,585
Recognition of credit claims as offset to research and development expense	21,130	17,564
Receipt of credit claims	(33,771)	(152)
Foreign currency translation	1,341	647
Balance at end of period	$ 17,344	$ 28,644

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, 2020, the Company's tax credit receivable from the UK was $17.3 million, all of which was classified as current. As of December 31, 2019, the Company's tax incentive receivable from the UK was $28.6 million, of which $14.9 million was classified as current and $13.7 million was classified as non-current. As of December 31, 2020, the Company has received all of its 2016-2019 tax credit claims from HMRC.

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 of Strimvelis are 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.

Net income (loss) per share

Basic net income (loss) per share is computed by dividing the net income (loss) by the weighted average number of ordinary shares outstanding for the period. Diluted net income (loss) is computed by adjusting net income (loss) based on the potential impact of dilutive securities. Diluted net income (loss) per share is computed by dividing the diluted net income (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:

	December 31,	
	2020	2019
Share options	11,071,555	10,056,864
Unvested shares from share plan and consulting agreement	816,316	751,496
	11,887,871	10,808,360

Recent accounting pronouncements

In February 2016 and July 2018, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), ASU 2018-10, Codification Improvements to Topic 842, Leases ("ASU 2018-10") and ASU 2018-11, Leases (Topic 842) Targeted Improvements ("ASU 2018-11"), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). ASU 2016-02, ASU 2018-10 and ASU 2018-11, supersede the lease guidance under FASB ASC Topic 840, *Leases*, resulting in the creation of FASB ASC Topic 842, *Leases* ("ASC 842"). The new standard requires that all lessees (i) recognize, on the balance sheet, liabilities to remit lease payments and right-of-use assets, representing the right to use the underlying asset for the lease term for both finance and operating leases, and (ii) disclose qualitative and quantitative information about its leasing arrangements.

ASC 842 became effective for the Company in 2019. The Company adopted ASC 842 using the modified retrospective approach with an effective date of January 1, 2019 for leases that existed on that date. Prior period results continue to be presented under ASC 840 based on the accounting standards originally in effect for such periods. This standard provides a number of optional practical expedients in transition. The Company applied the package of practical expedients to leases that commenced prior to the effective date, whereby it elected not to reassess the following: (i) whether any expired or existing contracts contain leases; (ii) the lease classification for any expired or existing leases; and (iii) initial direct costs for any existing leases. The Company elected the short-term lease recognition exemption for all leases that qualify, where a right-of-use asset or lease liability will not be recognized for short term leases that have terms of one year or less.

The operating lease right-of-use assets and corresponding liabilities relate to existing facility operating leases in London, UK, Boston, Massachusetts, and the San Francisco Bay Area, California, as well as an embedded operating lease for research and development space at a contract manufacturing organization. The most significant effects of adoption were the recognition of material new right-of-use assets and corresponding liabilities on its consolidated balance sheet related to its existing facility operating leases (see Note 10). The adoption of this standard had a material impact on the Company's financial position but did not significantly affect the Company's results of operations or cash flows.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"), which requires entities to record expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities in unrealized loss positions, the new standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard became effective for us on January 1, 2020. This guidance did not have a significant impact on the Company's consolidated financial statements and related disclosures. The Company has a UK research and development tax credit receivable and trade receivables that are subject to this guidance. The Company has assessed whether it believes there is a current estimate of credit loss expected to be recorded for these receivables and concluded that any amount would not be significant and therefore the Company has not recorded any credit loss allowance for these receivables.

In December 2019, the FASB issued ASU No. 2019-12, *Simplifying the Accounting for Income Taxes (Topic 740)*, which removes certain exceptions to the general principles in Topic 740 – *Income Taxes* and improves consistent application of and simplifies GAAP for other areas of Topic 740 by clarifying and amending existing guidance. This ASU is effective for the Company beginning January 1, 2021 and interim periods within that year, with early adoption permitted. The Company is currently evaluating the effect of adopting this new accounting guidance.

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, 2020 and 2019 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, 2020 and 2019, 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, 2020:

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

The following table summarizes the Company's cash equivalents and marketable securities as of December 31, 2019:
:

	Fair Value Measurements as of December 31, 2019 Using:			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 202	$ —	$ —	$ 202
U.S. government securities	—	3,159	—	3,159
Commercial paper	—	9,792	—	9,792
Total cash equivalents	$ 202	$ 12,951	$ —	$ 13,153
Marketable securities				
Corporate bonds	$ —	$ 259,900	$ —	259,900
Commercial paper	—	46,037	—	46,037
Total marketable securities	$ —	$ 305,937	$ —	$ 305,937
Total	$ 202	$ 318,888	$ —	$ 319,090

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 level 2 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 level 2 cash equivalents and marketable securities as of December 31, 2019:

	Fair Value Measurements as of December 31, 2019 Using:			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. government securities	$ 3,159	$ —	$ —	3,159
Corporate bonds	259,669	285	(54)	259,900
Commercial paper	55,794	42	(7)	55,829
Total	$ 318,622	$ 327	$ (61)	$ 318,888

The following table summarizes the Company's available-for-sale marketable debt securities by contractual maturity, as of December 31, 2020 and 2019:

	2020	2019
Maturities in one year or less	$ 132,056	$ 250,490
Maturities between one and three years	10,757	68,398
Total	$ 142,813	$ 318,888

4. Revenue Recognition

During the years ended December 31, 2020 and 2019 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.

Costs to manufacture 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 minimal 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,	
	2020	2019
Prepaid external research and development expenses	$ 1,421	$ 1,121
Inventories	665	—
Other prepayments	4,930	2,800
VAT receivable	2,780	1,091
Construction deposit - current	1,552	—
Non-trade receivables	2,017	3,518
Total prepaid expenses and other current assets	$ 13,365	$ 8,530

6. Property and equipment

Property and equipment consist of the following:

	December 31,	
	2020	2019
Property and equipment:		
Lab equipment	$ 5,114	$ 6,377
Leasehold improvements	2,522	1,839
Furniture and fixtures	304	508
Office and IT equipment	763	184
Construction-in-progress	302	1,848
Property and equipment	$ 9,005	$ 10,756
Less: accumulated depreciation	(4,224)	(3,160)
Property and equipment, net	$ 4,781	$ 7,596

Depreciation expense for the years ended December 31, 2020 and 2019 was $2.0 million and $1.7 million, respectively.

7. Other assets

Other assets consist of the following:

	December 31, 2020	December 31, 2019
Intangible assets - license milestones	$ 3,076	$ —
Deferred tax assets	5,219	2,985
Deposits	1,144	1,108
Deferred financing costs	975	307
Other non-current assets	1,554	—
Construction deposits - long-term	6,572	—
Total other assets	$ 18,540	$ 4,400

8. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31, 2020	December 31, 2019
Accrued external research and development expenses	$ 8,878	$ 16,215
Accrued payroll and related expenses	11,881	12,381
Accrued professional fees	791	1,321
Accrued other	6,477	5,069
Strimvelis liability - current portion	916	2,994
Total accrued expenses and other current liabilities	$ 28,943	$ 37,980

9. 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 are 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, 2019.

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:

		Asset write-down
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 10). 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.

10. 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 $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 $1.7 million in 2020.

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 2020. The lease agreement includes annual rent escalation provisions.

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 $0.9 million in 2020. The lease agreement includes annual rent escalation provisions.

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 9) 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 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 sheet.

As of December 31, 2020, the carrying value of the Fremont Head Lease right-of-use asset was $10.5 million and the lease liability was $14.4 million related to the Fremont facility. 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 2021 and 2022. The Company continues to assess the expected receipt of the tenant improvement allowances any 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 $2.1 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 $8.1 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 $1.9 million in receipts from the escrow funds for costs incurred to date. Of the $8.1 million remaining in the escrow account, $1.6 million is classified within prepaid expenses and other current assets and $6.5 million is classified within other assets on the consolidated balance sheet 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 16). 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 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 with an initial annual commitment of €10.2 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, 2020 and 2019:

	2020	2019
Fixed lease cost	$ 7,593	$ 5,589
Impairment of right-of-use assets	$ 2,781	—
Variable lease cost	2,131	1,436
Sublease income	(181)	—
Total lease cost	$ 12,324	$ 7,025
Other information		
Operating cash flows used for operating leases	8,447	5,738
Weighted-average remaining lease term (years)	6.6	8.2
Weighted-average discount rate	8.6%	9.3%

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, 2020, the Company obtained right of use assets valued at $17.5 million in exchange for
lease liabilities of $17.5 million. During the year ended December 31, 2019 there were no material right of use assets obtained in exchange for material new lease obligations.

As of December 31, 2020, 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
2021	$ 8,941	$ (181)	$ 8,760
2022	8,093	(2,180)	5,913
2023	7,043	(2,245)	4,798
2024	7,067	(2,312)	4,755
2025	4,657	(2,382)	2,275
Thereafter	15,053	(11,413)	3,640
Total future minimum lease payments	50,854	(20,713)	30,141
Less: imputed interest	(17,752)		
Total operating lease payments	$ 33,102		

*Tabular disclosure above for leases denominated in GBP have been translated at a rate of £1.00 to $1.36, and leases denominated in Euro have been translated at a rate of €1.00 to $1.23.

11. Notes Payable

In May 2019, as amended in April 2020, the Company entered into a senior term facilities agreement (the "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. To date, the Company has borrowed $25.0 million under an initial term loan. The remaining $50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a $25.0 million term loan available no earlier than July 1, 2020 and no later than March 31, 2021 upon submission of certain regulatory filings and evidence of the Company having $100.0 million in cash and cash equivalent investments; and the third term loan being a $25.0 million term loan available no earlier than July 1, 2020 and no later than September 30, 2021 upon certain regulatory approvals and evidence of the Company having $125.0 million in cash and cash equivalent investments. As of December 31, 2020, the Company had met the criteria to draw down the second and third term loans totaling $50.0 million.

The term loans under the Credit Facility will terminate on the fifth anniversary of the Closing Date (the "Loan Maturity Date"). Each term loan under the Credit Facility bears interest at an annual rate equal to 6% plus LIBOR. The Company is required to make interest-only payments on the term loan for all payment dates prior to 24 months following the date of the Credit Facility, unless the third tranche is drawn, in which case the Company is required to make interest-only payments for all payment dates prior to 36 months following the date of the Credit Facility. The term loans under the Credit Facility will begin amortizing on either the 24-month or the 36-month anniversary of the 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 4.5% is due on the Loan Maturity Date. The Company accrues the final payment amount of $1.1 million associated with the first term loan, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the maturity date.

The 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, 2020 and 2019, notes payable consist of the following:

	December 31,	
	2020	2019
Notes payable, net of issuance costs	$ 24,659	$ 24,541
Less: current portion	$ (4,861)	—
Notes payable, net of current portion	19,798	24,541
Accretion related to final payment	406	158
Notes payable, long term	$ 20,204	$ 24,699

As of December 31, 2020, the future principal payments due are as follows:

	Aggregate Minimum Payments
2021	4,861
2022	8,333
2023	8,334
2024	4,597
2025	—
Thereafter	—
Total	26,125
Less current portion	(4,861)
Less unamortized portion of final payment	(719)
Less unamortized debt issuance costs	(341)
Notes payable, long term	$ 20,204

During the years ended December 31, 2020 and 2019, the Company recognized $2.3 million and $1.5 million of interest expense related to the term loan, respectively. The effective annual interest rate as of December 31, 2020 on the outstanding debt under the Term Loan was approximately 9.3%.

12. Shareholders' Equity and Convertible Preferred Shares

Ordinary shares

As of December 31, 2020, and 2019, 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, 2020, and 2019, the Company has not declared any dividends.

As of December 31, 2020, and 2019, 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 June 2019, the Company completed its follow-on public offering of ADSs. The Company sold an aggregate of 9,725,268 ADSs representing the same number of ordinary shares at a public offering price of $14.25 per ADS, including a partial exercise by the underwriters of their option to purchase additional ADSs. Net proceeds were

$129.7 million, after deducting underwriting discounts of $8.3 million, and commissions and offering expenses paid by the Company of $0.6 million.

In April 2020, the Company issued 75,413 ordinary shares to Oxford BioMedica pursuant to the terms of our license agreement (see Note 14).

In December 2020, the Company issued 22,758 ordinary shares pursuant to a consulting agreement (see Note 16) with a non-employee advisor.

13. 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, 2020, 6,611,693 shares remained available for grant under the 2018 Plan, 1,000,000 remained available under the Inducement Plan, and 1,470,104 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,	
	2020	2019
Risk-free interest rate	0.3 - 1.7%	1.4 - 2.6%
Expected term (in years)	5.5 - 6.1	5.5 - 6.1
Expected volatility	70.7 - 75.2%	70.1 - 72.1%
Expected dividend rate	0.00%	0.00%

The following table summarizes option activity under the plans for the year ended December 31, 2020:

	Shares	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2019	12,216,140	$ 6.61	8.31	$ 91,133
Granted	5,846,152	11.37		
Exercised	(1,154,441)	2.99		
Forfeited	(3,012,208)	10.99		
Outstanding and expected to vest at December 31, 2020	13,895,643	$ 7.96	7.16	$ 15,473
Exercisable, as of December 31, 2020	7,120,307	$ 5.98	5.73	$ 12,318

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, 2020 and 2019, the total intrinsic value of share options exercised was $5.0 million and $17.2 million, respectively. During the years ended December 31, 2020 and 2019, the total proceeds to the Company from share options exercised was $3.9 million and $2.0 million, respectively. As of December 31, 2020, and 2019, there was $0.2 million and nil 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, 2020 and 2019 was $7.22 per shares and $8.67 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. No performance-based share units vested during the years ended December 31, 2020 or 2019.

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. The amount of compensation cost recognized for the years ended December 31, 2020 and 2019 for the market condition associated with the performance-based RSUs was $0.3 million and $1.2 million, respectively.

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, 2020.

Time-based restricted share units

Time-based restricted share units general 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, 2020:

	Shares	Weighted Average Fair Value per Share
Unvested at December 31, 2019	556,422	$ 13.58
Granted	426,750	6.42
Vested	—	—
Forfeited	(339,172)	13.75
Unvested at December 31, 2020	644,000	$ 8.75

Share-based compensation

Share-based compensation expense related to share options, restricted share unit awards, and the employee stock purchase plan was classified in the consolidated statements of operations and comprehensive loss as follows:

	Year Ended December 31,	
	2020	2019
Research and development	$ 11,679	$ 7,425
Selling, general and administrative	16,283	11,999
Total	$ 27,962	$ 19,424

The Company had 6,775,336 unvested options outstanding as of December 31, 2020. As of December 31, 2020, total unrecognized compensation cost related to unvested stock option grants and time-based RSUs was approximately $46.4 million. This amount is expected to be recognized over a weighted average period of approximately 2.52 years. As of December 31, 2020, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $4.0 million, dependent upon achievement of milestones.

14. 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, 2020, the Company does not consider the attainment of a PRV from the United States Food and Drug Administration to be probable.

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as the Company's OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a liability associated with the loss contract of £12.9 million ($18.4 million at the acquisition date) associated with the loss expected due to this obligation. This liability is being amortized over the remaining period of expected sales of Strimvelis as a credit to research and development expenses (see Note 2).

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and the Company-developed product candidate, OTL-101. The Company will also pay tiered royalty rates at a percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at 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 16).

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 ($38.1 million at December 31, 2020) 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 ($34.4 million at December 31, 2020). 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 upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

The Company recorded $0.1 million of research and development costs in respect of the UCLB/UCLA license agreement, which comprise the upfront payments, issuance of ordinary shares and payments for clinical data, for each of the years ended December 31, 2020 and 2019.

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, 2019.

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

15. Income Taxes

The components of income (loss) from operations before income taxes for the years ended December 31, 2020 and 2019 are as follows:

	December 31,	
	2020	2019
UK	$ (155,614)	$ (173,118)
Non-UK	2,904	7,456
Loss before taxes	$ (152,710)	$ (165,662)

The (benefit from) provision for income taxes for the years ended December 31, 2020 and 2019 are as follows:

	December 31,	
	2020	2019
Current (benefit) provision		
Federal—United States	$ 1,107	$ 888
State—United States	189	(275)
Other foreign	230	89
Total current (benefit) provision	1,526	702
Deferred (benefit) provision		
Federal—United States	(1,774)	(2,820)
State—United States	(103)	(122)
Other foreign	(380)	—
Total deferred (benefit) provision	(2,257)	(2,942)
Total (benefit) provision for income taxes	$ (731)	$ (2,240)

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

	December 31,	
	2020	2019
Income taxes at United Kingdom statutory rate	$ (29,015)	$ (31,475)
Change in valuation allowance	29,302	16,507
Reduction in research expense for credits granted	8,435	9,787
Change in tax rates	(8,105)	8,109
Tax credits	(1,369)	(3,372)
U.S. Deduction for foreign derived intangible income	(1,254)	(2,058)
Permanent differences, including share-based compensation deduction shortfalls	1,265	344
U.S. state income taxes	68	(238)
Foreign rate differential	(58)	156
Total (benefit) provision for income taxes	$ (731)	$ (2,240)

The Company's income tax benefit for the year ended December 31, 2020 compared to the year ended December 31, 2019 decreased primarily related to shortfall of tax deduction from share-based compensation and reduction of U.S. deduction for foreign derived intangible income ("FDII") and U.S. federal research and development tax credits.

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, 2020 and 2019:

	December 31,	
	2020	2019
Deferred tax assets		
Net operating loss carryforwards	$ 75,502	$ 45,358
Amortization	22,599	21,741
Research and development credits	1,564	1,244
Share-based compensation	7,400	3,604
Accruals	1,001	1,286
Lease Liability	6,805	4,406
Other	3	1
Total deferred tax assets	114,874	77,640
Valuation allowance	(103,890)	(70,153)
Fixed assets and right-of-use asset	(5,765)	(4,502)
Other non-current assets (net deferred tax assets and liabilities)	$ 5,219	$ 2,985

For the years ended December 31, 2020 and 2019, the Company had cumulative UK net operating loss carryforwards of approximately $390.1 million and $266.8 million, respectively. Unsurrendered UK losses may be carried forward indefinitely, subject to numerous utilization criteria and restrictions and are fully offset by a valuation allowance.

For the year ended December 31, 2020, the Company had cumulative U.S. federal general business and U.S. state research and development tax credit carryforwards of approximately $2.0 million available to reduce future U.S. state tax liabilities. The U.S. state tax credit carryforwards can be carried forward indefinitely and are fully 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, we consider new evidence, both positive and negative, that could impact our 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, 2020 and 2019, respectively.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2020 and 2019 related primarily to the increase in UK net operating loss carryforwards and UK amortization of intangible assets and were as follows:

	December 31,	
	2020	2019
Valuation allowance as of beginning of year	$ (70,153)	$ (51,281)
Decreases recorded as benefit to income tax provision	—	—
Increases recorded to income tax provision	(29,302)	(16,507)
Effect of foreign currency translation	(4,435)	(2,365)
Valuation allowance as of end of year	$ (103,890)	$ (70,153)

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, 2020 and 2019.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense when in a taxable income position. As of December 31, 2020, and 2019, 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 2020 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.

16. Commitments and Contingencies

Lease commitments

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

Manufacturing and technology development master agreement with AGC

As discussed in Note 10, 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, 2020:

Due in:	Product manufacturing commitments (1)	Dedicated manufacturing and development resources (2)	Exclusive transduction suites (3)	Total AGC Commitment
2021	$ 2,491	$ 8,524	$ 4,190	$ 15,205
2022	3,321	8,524	3,352	15,197
2023	3,321	8,524	3,352	15,197
2024	3,321	8,524	3,352	15,197
2025	1,661	4,262	838	6,761
Thereafter	—	—	—	—
Total manufacturing commitments	$ 14,115	$ 38,358	$ 15,084	$ 67,557

*Tabular disclosure above has been translated to U.S. Dollar, from Euro, using an exchange rate of €1.00 to $1.23.

(1) The minimum product manufacturing commitments may be increased to the mid-seven figures per contract year upon achievement of certain milestones.
(2) The Company may increase or decrease the usage of dedicated development services on a rolling basis with between six and 12-months' prior written notice to AGC. The above table assumes continued usage of dedicated development services at current rates.
(3) Refer to Note 10 for further information on the embedded operating lease agreement

The 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 14). 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 2020, the Company issued 22,758 ordinary shares associated with the service condition.

During the years ended December 31, 2020 and 2019, the Company recorded $0.3 million and nil in research and development expense associated with the share-based awards with service conditions. During the years ended December 31, 2020 and 2019, 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.

17. 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 $1.6 million and $1.3 million, in matching contributions for the years ended December 31, 2020 and 2019, respectively.

18. 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 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.

During the year-ended December 31, 2019, the Company made $7.2 million in payments to settle accounts payable due to GSK associated with the TSA and royalties associated with sales of Strimvelis incurred during 2018. Additionally, during 2019, the Company made a $3.6 million payment associated with the inventory purchase liability incurred upon entering into the agreement, and $0.1 million in royalties associated with Strimvelis sales during the year. As of December 31, 2019, the Company had inventory purchase liability in accrued research and development expenses of $3.3 million.

19. Selected Quarterly Financial Information (unaudited)

The following tables summarizes the unaudited quarterly financial data for the last two fiscal years:

	2020				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Full year
Total revenues	$ —	$ 597	$ 1,998	$ —	$ 2,595
Total costs and operating expenses	44,981	47,418	28,301	38,873	159,573
Loss from operations	(44,981)	(46,821)	(26,303)	(38,873)	(156,978)
Net loss attributable to ordinary shareholders	(50,569)	(47,500)	(20,290)	(33,620)	(151,979)
Weighted average ordinary shares outstanding - basic and diluted	98,713,126	99,251,314	99,664,616	100,013,246	99,445,874
Earnings per share	$ (0.51)	$ (0.48)	$ (0.20)	$ (0.34)	$ (1.53)

	2019				
	First Quarter	Second Quarter (2)	Third Quarter	Fourth Quarter	Full year
Total revenues	$ —	$ —	$ 1,918	$ 595	$ 2,513
Total costs and operating expenses	28,283	54,152	43,330	49,621	175,386
Loss from operations	(28,283)	(54,152)	(41,412)	(49,026)	(172,873)
Net loss attributable to ordinary shareholders	(30,739)	(50,530)	(36,737)	(45,416)	(163,422)
Weighted average ordinary shares outstanding - basic and diluted	87,010,596	89,712,916	97,817,847	98,243,915	93,240,355
Earnings per share	$ (0.35)	$ (0.56)	$ (0.38)	$ (0.46)	$ (1.75)

20. Subsequent Events

Securities Purchase Agreement

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 (the "Private Placement"). The Private Placement resulted in gross proceeds to the Company of $150.0 million before deducting placement agent fees of $6.0 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.