Orchard Therapeutics plc

Annual Report and Financial Statements
for the Year Ended 31 December 2021

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 Joanne Beck John Curnutte Marc Dunoyer Jon Ellis (Resigned 16 June 2021) Hubert Gaspar Charles Rowland Alicia Secor
Secretary	Christopher York
Registered Office	108 Cannon Street London EC4N 6EU United Kingdom
Company Number	11494381
Independent Auditors	PricewaterhouseCoopers LLP 40 Clarendon Road Watford WD17 1JJ 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. The consolidated financial statements comprise both the consolidated financial statements of Orchard Therapeutics plc on Form 10-K from page 119 onwards, and the certain note disclosures relevant to the Group financial statements on this page.

UK Statutory Disclosure Requirements

(i) Monthly average number of people employed

	Number of People	
Group	2021	2020
UK	146	125
Offshore	92	125
Total employees	**238**	**250**

The monthly average number of people employed by the Parent Company (including Directors) in 2021 was 7 (2020: 8), which is comprised solely of the Directors of the Company.

(ii) Employee costs (in thousands)

Group	2021 ($ USD)	2020 ($ USD)
Salaries and bonuses	43,804	49,242
Share-based compensation expense	22,536	27,971
Benefits	2,419	3,271
Defined contribution scheme contributions	1,736	1,656
Social insurance and social security costs	3,209	4,951
Total employee costs	**73,704**	**87,091**

The Parent Company does not have any employees. During fiscal year 2021, the Parent Company had $1,751k in share-based compensation expense associated with equity awards granted to Non-Executive Directors (2020: $2,661k).

(iii) Auditors' remuneration

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

Group	2021 ($ USD)	2020 ($ USD)
Fees payable to the Company's auditors for the audit of the Company and consolidated financial statements for the year ended December 31	1,233	1,199
Audit-related assurance services	118	222
Accounting research tool subscriptions	5	3
Total fees paid to PricewaterhouseCoopers LLP	**1,356**	**1,424**

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 2022 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 2021 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 2021; 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 eight 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 99.4% of group assets and 93.3% of the group loss.

Key audit matters

- Orchard Therapeutics (Europe) Limited Research & Development Tax Credit Receivable

Materiality

- Overall materiality: US$7,250,000 (2020: US$8,000,000) based on 5% of loss before tax.
- Performance materiality: US$5,400,000 (2020: US$6,000,000).

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.

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.

Impact of Covid-19, which was a key audit matter last year, is no longer included because the impact of Covid-19 on the Group has significantly reduced in the year. Otherwise, the key audit matter below is consistent with last year.

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 2021, the Company recorded $13.9 million as a reduction of research and development expense related to these programs and has a related tax credit receivable of $30.7 million as of 31 December 2021. 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.

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 eight 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 relied on the work performed by PwC US over Orchard Therapeutics North America and Orchard Therapeutics plc, along with certain procedures over Orchard Therapeutics (Europe) Limited, in addition to the work performed by PwC UK over Orchard Therapeutics (Europe) Limited and the consolidation. 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 restricted throughout 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$7,250,000 (2020: US$8,000,000).
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 $6.3 million to $6.7 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% (2020: 75%) of overall materiality, amounting to US$5,400,000 (2020: US$6,000,000) 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 in the middle 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 $360,000 (2020: $400,000) 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:

- Assessing management's latest cash flow forecast, in which we have assessed the forecasts for reasonableness, understanding the planned cash outflows/inflows and considering management's previous ability to forecast accurately. 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 reduced.

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.

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 2021 is consistent with the financial statements and has been prepared in accordance with applicable legal requirements.

continued

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.

Irregularities, including fraud, are instances of non-compliance with laws and regulations. We design procedures in line with our responsibilities, outlined above, 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 clinical 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 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.

continued

- 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.

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.

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 2021 and on the information in the Directors' Remuneration Report that is described as having been audited.

Katherine Birch-Evans

Katherine Birch-Evans (Senior Statutory Auditor)
for and on behalf of PricewaterhouseCoopers LLP
Chartered Accountants and Statutory Auditors
Watford

25 April 2022

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 2021 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 2021; 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

Valuation of investment in Orchard Therapeutics (Europe) Limited and recoverability of intercompany receivable

Materiality

- Overall materiality: US$2,042,000 (2020: US$4,546,000) based on 1% of total assets.
- Performance materiality: US$1,532,000 (2020: US$3,410,000).

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

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.

Impact of Covid-19, which was a key audit matter last year, is no longer included because the impact of Covid-19 on the Group has significantly reduced in the year. Otherwise, the valuation of investment in Orchard Therapeutics (Europe) Limited element of the key audit matter below is consistent with last year, but the recoverability of intercompany receivable element is new this year.

Key audit matter	**How our audit addressed the key audit matter**
Valuation of investment in Orchard Therapeutics (Europe) Limited and recoverability of intercompany receivable The parent company holds an investment in its subsidiary, Orchard Therapeutics (Europe) Limited, and has an intercompany receivable due from this subsidiary. The reduction in the market capitalisation of Orchard Therapeutics plc, based on the Group's share price at 31 December 2021, is an indicator of potential impairment of both the investment and the intercompany receivable held by the parent company. The market capitalisation of the Group at 31 December 2021 is below the carrying value of the investment and intercompany receivable due from Orchard Therapeutics (Europe) Limited. Because of the uncertainties involved in a value in use calculation, management assessed the market capitalisation of the Group, adjusted for the parent company's net assets, to be representative of the fair value less costs of disposal of the investment and intercompany receivable, and therefore the realisable value of the subsidiary. When comparing the fair value less costs to sell to the carrying value of the investment and intercompany receivable an impairment charge of $427m is required. A $306m charge has been recognised against the investment to impair this to nil, with the remaining $121m against the intercompany receivable, to impair this down to the realisable value of the subsidiary.	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), including an assessment of the reasonableness of the fair value less costs of disposal approached adopted by management. – 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 and intercompany receivable over their recoverable amounts, which is determined using a fair value less costs to sell method. – Reviewed the disclosures in the financial statements. The methodology adopted by management and the conclusions reached are deemed to be reasonable and appropriate.

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 have instructed PwC US to report on the special purpose financial information of the parent company 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$2,042,000 (2020: US$4,546,000).
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% (2020: 75%) of overall materiality, amounting to US$1,532,000 (2020: US$3,410,000) 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 in the middle 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 $102,000 (2020: $243,000) as well as misstatements below that amount that, in our view, warranted reporting for qualitative reasons.

continued

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:

- Assessing management's latest cash flow forecast, in which we have assessed the forecasts for reasonableness, understanding the planned cash outflows/inflows and considering management's previous ability to forecast accurately. 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 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 2021 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.

continued

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.

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.

Irregularities, including fraud, are instances of non-compliance with laws and regulations. We design procedures in line with our responsibilities, outlined above, 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 UK incorporated company which is listed in the US, 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 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 meetings 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.

continued

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.

Other matter

We have reported separately on the group financial statements of Orchard Therapeutics plc for the year ended 31 December 2021.

Katherine Birch-Evans

Katherine Birch-Evans (Senior Statutory Auditor)
for and on behalf of PricewaterhouseCoopers LLP
Chartered Accountants and Statutory Auditors
Watford

25 April 2022

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 the 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 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 also 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 2021. 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 2021, 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 Initial Public Offering ("IPO") and follow-on offering, proceeds from the sale of ordinary shares in our private placement, proceeds from the sale of convertible preferred shares, proceeds associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program, reimbursements from our research agreement with University of California Los Angeles ("UCLA") and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., and our Original Credit Facility and our Amended Credit Facility.

On 27 February 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 31 December 2021, we have not sold any shares under the Sales Agreement. On 24 March 2022, we delivered written notice to Cowen to terminate the Sales Agreement, effective as of 30 March 2022, pursuant to Section 11(b) thereof. We are not subject to any termination penalties related to the termination of the Sales Agreement. Prior to termination, we had not sold any ADSs pursuant to the Sales Agreement. As a result of the termination of the Sales Agreement, we will not offer or sell any ADSs under the Sales Agreement.

On 9 February 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 4 February 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 4 February 2021.

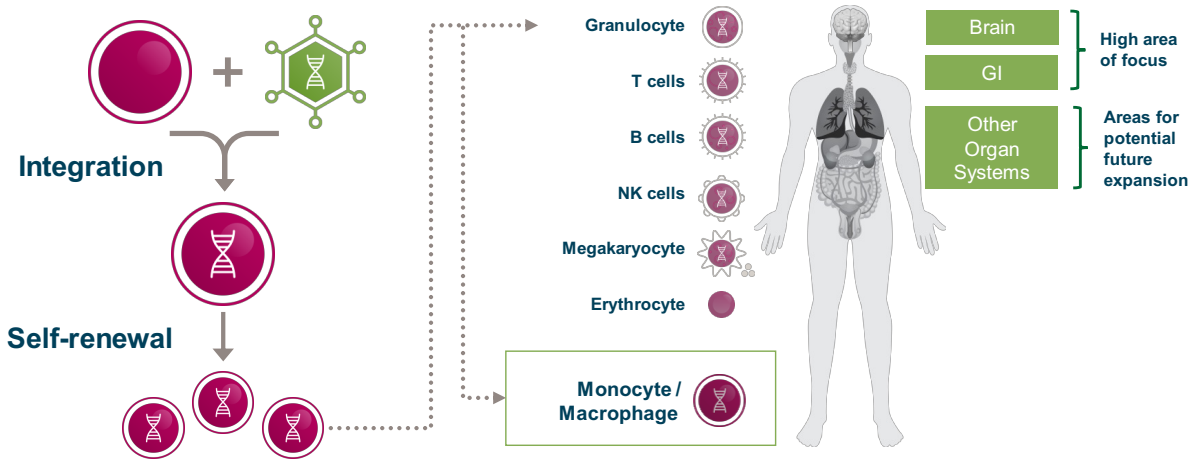
Business Overview (including company strategy, business model, and key performance indicators)

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

We are currently focusing our *ex vivo* autologous HSC gene therapy approach on severe neurometabolic diseases and early research programs. Our lead program is OTL-200, which was approved in the European Union, the United Kingdom, Iceland, Liechtenstein and Norway under the brand name Libmeldy for eligible patients with early-onset metachromatic leukodystrophy, or MLD. Three eligible patients have been treated in a commercial setting to date. Our planned biologics license application ("BLA") submission timeline for OTL-200 with the Food and Drug Administration ("FDA") is late 2022 to early 2023.

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



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

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

With the exception of OTL-105, our product candidate for the potential treatment of hereditary angioedema, or HAE, which we are pursuing in partnership with Pharming Group N.V., we have global commercial rights to all our clinical product candidates and plan to commercialise our gene therapies in key markets worldwide, including in Europe and the U.S. initially, subject to obtaining the necessary marketing approvals for these jurisdictions. We plan to deploy a focused commercial infrastructure to deliver Libmeldy and our product candidates, if approved, to patients and are focused on working closely with all relevant stakeholders, including patients, caregivers, specialist physicians and payors, to ensure the widest possible post-approval access for our product candidates. In addition, we may rely on third parties to assist with regulatory submissions, disease awareness, patient identification and reimbursement in countries where local expertise is required or where we do not have a direct presence. For example, in January 2021, we announced partnerships with two regional specialty pharmaceutical companies with experience in rare genetic diseases to support us in the Middle East and Turkey.

As we continue to develop our portfolio, we believe that the experience of our management team and our extensive academic relationships are key strategic strengths. Our management team has extensive experience in rare diseases and in the manufacturing, preclinical and clinical development and commercialisation 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 commercialisation and continue to expand our portfolio of *ex vivo* autologous HSC gene therapy products.

Our *ex vivo* autologous HSC gene therapy approach

Our *ex vivo* autologous HSC gene therapy approach seeks to transform a patient's autologous HSCs into a gene-modified cellular drug product to treat the patient's disease. HSCs are self-renewing cells that are capable of differentiating into all types of blood cells, including white blood cells, red blood cells, platelets and tissue resident macrophages, which include the microglia of the central nervous system. HSCs can be obtained directly from the bone marrow, which requires administration of a general anesthetic, or from the patient's peripheral blood with the use of mobilizing agents, which are agents that can move HSCs from the bone marrow into the peripheral blood for easier collection. The HSCs collected are then manufactured to insert a functional copy of the missing or faulty gene. By delivering gene-modified HSCs back to patients, we seek to take advantage of the self-renewing capability of HSCs to enable a durable effect following a single administration, as has been seen in our commercial and development programs. Since these cells are recognized by the body as the

patient's own cells, the risks associated with using donor cells may be reduced. In addition, the ability of HSCs to differentiate into multiple different cell types has the potential to enable the delivery of gene-modified cells to different physiological systems and allow the correction of a broad range of different diseases.

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

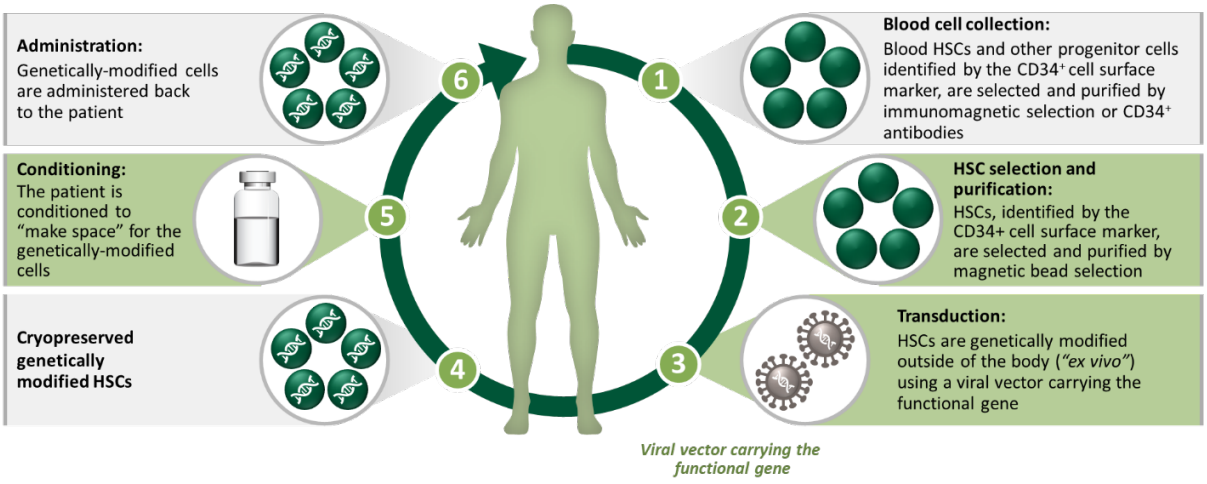
In a preclinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America*, or *PNAS*, a subpopulation of gene-modified HSCs has evidenced the potential to cross the blood-brain barrier, engraft in the brain as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

With respect to Libmeldy (OTL-200) and each of our product candidates, our *ex vivo* gene therapy approach utilizes a self-inactivating, or SIN, lentiviral vector to introduce a functional copy of the missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process called transduction, resulting in a cellular drug product that can then be re-introduced into the patient. Unlike some other viral vectors, such as adeno-associated viral, or AAV, vectors, lentiviral vectors integrate into the chromosomes of patients' HSCs. We believe this allows us to achieve stable integration of the functional gene into the HSCs and can lead to durable expression of the target protein by the gene-modified HSCs and their progeny after a single administration of gene therapy. In contrast, because AAV vectors rarely integrate into the genome, the transgene is not passed on to all progeny when the cell divides, resulting in rapid dilution and loss of the transgene among frequently dividing cells such as HSCs. Regarding immunogenicity, because in vivo delivery of AAV places the vector into direct contact with the immune system and most individuals harbor some type of pre-existing immunity, including neutralizing antibodies, to one or more types of AAV vector, the incoming vector can be completely inactivated by the patient's immune system. Furthermore, there have been reports that certain high dose applications of AAV have resulted in acute and severe innate immune responses that have proved lethal. With *ex vivo* delivery, however, the vector is not introduced directly into the body and vector elements are washed away in the laboratory such that there is little to no

vector element left to present to the immune system. Our HSC gene therapies and product candidates are all manufactured *ex vivo*.

Strimvelis for adenosine deaminase severe combined immunodeficiency, or ADA-SCID, is the only gammaretroviral vector-based gene therapy in our portfolio.

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



Initial clinical trials conducted using our product candidates utilized a fresh product formulation, resulting in a limited drug product shelf life. We market Libmeldy (OTL-200) and plan to market our current and any future product candidates, if approved, in a cryopreserved product formulation, which is designed to extend the drug product shelf life and enable the shipment of the drug product to specialized treatment centers, allowing patients to receive treatment closer to their home while leveraging more centralized manufacturing. Cryopreservation also allows us to conduct a number of quality control tests on the genetically modified HSCs prior to introducing them into the patient.

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

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

Our strategy

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

- Successfully commercialise Libmeldy (OTL-200) for the treatment of eligible patients with early-onset MLD in Europe and expand geographically into new markets as regulatory approvals are obtained
- Advance our clinical-stage product candidates towards marketing approvals
- Leverage the power of our therapeutic approach to investigate the potential of HSC gene therapy in larger indications
- Invest in new technologies and innovations to continue to improve our manufacturing processes for lentiviral vector and drug product and reduce costs of goods manufactured
- Establish end-to-end process development, manufacturing and supply chain capabilities, initially through third parties and internally over time
- Establish a patient-centric, global commercial infrastructure, including with third parties in certain regions where we do not have a direct presence
- Execute a business development strategy to leverage our HSC gene therapy approach, expand geographically, accelerate time-to-market or attract disease-area expertise to optimize the value of our portfolio of product candidates or expand into new indications

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

Our pipeline

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

- Our programs focused on neurodegenerative disorders consist of our commercial program approved in Europe, Libmeldy (OTL-200) for MLD, two clinical proof of concept-stage programs, OTL-203 for MPS-I and OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, and three preclinical programs, OTL-202 for mucopolysaccharidosis type IIIB, or MPS-IIIB, OTL-204 for frontotemporal dementia with progranulin mutations, or GRN-FTD, and OTL-205 for amyotrophic lateral sclerosis, or ALS.
- Our programs in immunological disorders consist of two preclinical programs, OTL-104 for Crohn's disease with mutations in the nucleotide-binding oligomerization domain-containing protein 2, or NOD2-CD, and OTL-105 for HAE.
  - We also have a commercial program approved in Europe, Strimvelis for adenosine deaminase severe combined immunodeficiency, or ADA-SCID, an advanced registrational clinical program, OTL-103 for Wiskott Aldrich syndrome, or WAS, and one clinical proof of concept-stage program, OTL-102 for X-linked chronic granulomatous disease, or X-CGD. However, in March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis, OTL-103 and OTL-102.

- In July 2021, we entered into a collaboration with Pharming Group N.V., or Pharming, pursuant to which we granted Pharming worldwide rights to OTL-105. Under our agreement with Pharming, we will lead the completion of Investigational New Drug Application ("IND") enabling activities of OTL-105 and oversee its manufacturing during pre-clinical and clinical development, which will be funded by Pharming. Pharming will be responsible for clinical development, regulatory filings and commercialisation of OTL-105, if approved, including associated costs.

• We have a program focused on blood disorders at the clinical proof of concept stage of development, OTL-300 for TDT. However, in May 2020, we announced that new investment in OTL-300 would be limited.

The nature of our autologous gene therapy product candidates precludes the conduct of Phase 1 safety studies in healthy volunteers. Moreover, considering the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare indications with high unmet medical need, we believe our clinical programs will generally be eligible to proceed to registration based on a single pivotal study given the bioethical considerations regarding the conduct of randomized, double-blind and placebo-controlled clinical trials with gene therapies for such indications. For purposes of this Annual Report, we refer to an exploratory study, which is sometimes referred to as a Phase 1 or Phase 1/2 clinical trial, as a proof of concept trial, and a confirmatory efficacy and safety study to support submission of a potential marketing application with the applicable regulatory authorities, which is sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial, as a registrational trial.

Neurodegenerative Disorders

Gene therapy for treatment of MLD

Disease overview

MLD is a rare and life-threatening inherited disease of the body's metabolic system occurring in approximately one in every 100,000 live births in most regions of the world. Higher incidence rates are reported in geographies of higher consanguinity, such as Turkey and the Middle East. MLD is caused by a mutation in the arylsulfatase-A gene, or ARSA, that results in the accumulation of sulfatides in the brain and other areas of the body, including the liver, gallbladder, kidneys, and/or spleen. Over time, the nervous system is damaged, leading to neurological problems such as motor, behavioral and cognitive regression, severe spasticity and seizures. Patients with MLD gradually lose the ability to move, talk, swallow, eat and see. In its late infantile form, mortality at five years from onset is estimated at 50% and 44% at 10 years for juvenile patients.

Limitations of current therapies

Prior to the approval of Libmeldy (OTL-200) in Europe, there were no effective treatments or approved therapies for MLD. Palliative care options involve medications for seizures and pain, antibiotics and sedatives, on a case-by-case basis, as well as physiotherapy, hydrotherapy and tube feeding or gastrostomy when patients can no longer eat without assistance. Palliative care addresses the symptoms of MLD but does not slow or reverse the progression of the underlying disease. HSCT has limited and variable efficacy in arresting disease progression and, as a result, HSCT is not considered to be a standard of care for this disease. MLD patients, their caregivers and families, and the healthcare system have faced significant burdens given the severity of the disease and the lack of effective treatments.

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

OTL-200 is designed as a one-time therapy that aims to correct the underlying genetic cause of MLD, offering eligible patients the potential for long-term positive effects on cognitive development and

maintenance of motor function at ages at which untreated patients show severe motor and cognitive impairments. With OTL-200, a patient's own HSCs are selected, and functional copies of the ARSA gene are inserted into the genome of the HSCs using a lentiviral vector before these genetically modified cells are infused back into the patient. The ability of the gene-corrected HSCs to migrate across the blood-brain barrier into the brain, engraft, and express the functional enzyme has the potential to persistently correct the underlying disease with a single treatment.

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

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 timepoints in order to further characterize the long-term efficacy and safety of Libmeldy, particularly in the early symptomatic early juvenile population.

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

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

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

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

- 29 patients from integrated efficacy analysis (described above)
- 6 patients treated with the cryopreserved formulation of Libmeldy

Co-primary endpoints
The co-primary endpoints of the integrated efficacy analysis were Gross Motor Function Measure, or GMFM, total score and ARSA activity, both evaluated at two years post-treatment. Results of this

analysis indicate that a single-dose intravenous administration of Libmeldy is effective in modifying the disease course of early-onset MLD in most patients.

Pre-symptomatic LI and EJ patients treated with Libmeldy experienced significantly less deterioration in motor function at two years and three years post-treatment, as measured by GMFM total score, compared to age and disease subtype-matched untreated patients ($p \leq 0.008$). The mean difference between treated pre-symptomatic LI patients and age-matched untreated LI patients was 71.0% at year 2 and 79.8% at year 3. Similarly, the mean difference between treated pre-symptomatic EJ patients and age-matched untreated EJ patients was 52.4% at year 2 and 74.9% at year 3. Although not statistically significant, a clear difference in GMFM total score was also noted between treated early-symptomatic EJ patients and age-matched untreated EJ patients (28.7% at year 2; $p=0.350$ and 43.9% at year 3; $p=0.054$).

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

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

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

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

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

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

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

Data Supporting Safety Profile of Libmeldy
The safety of Libmeldy was evaluated in 35 patients with MLD.

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

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

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

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

OTL-200 development in the U.S.
OTL-200 has received orphan drug designation for the treatment of MLD as well as Rare Pediatric Disease designation. In late 2020, the FDA cleared our IND application for OTL-200 in the U.S., and in January 2021, FDA granted regenerative medicine advanced therapy, or RMAT, designation for OTL-200. Based on feedback received from the FDA, we are preparing for a BLA filing for OTL-200 in pre-symptomatic, early-onset MLD patients in late 2022 or early 2023 using data from existing OTL-200 patients. This approach and timeline are subject to the successful completion of activities remaining in advance of an expected pre-BLA meeting with the FDA, including demonstration of the natural history data as a representative comparator for the treated population.

Gene therapy for treatment of MPS-I
Disease overview
Mucopolysaccharidosis type I is a lysosomal storage disease caused by a deficiency of the lysosomal enzyme alpha-L-iduronidase, or IDUA. Inherited deficiency of IDUA is responsible for MPS-I. Without treatment, clinical manifestations of this severe disease include skeletal abnormalities with severe orthopedic manifestations, hepatosplenomegaly, neurodevelopmental decline, sight and hearing disturbances, cardiovascular and respiratory problems leading to death in early childhood. IDUA

deficiency can result in a wide range of clinical severity, with 3 major recognized clinical entities: Hurler, or MPS-IH, Scheie, or MPS-IS, and Hurler-Scheie, or MPS-IH/S, syndromes. Hurler and Scheie syndromes represent phenotypes at the severe and attenuated ends of the MPS-I clinical spectrum, respectively.

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

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

Limitations of current therapies
Allogeneic-HSCT with pre- and peri-transplant enzyme replacement therapy, or ERT, from diagnosis to engraftment has been established as the standard of care for MPS-IH patients diagnosed before the age of 30 months and with presumed MPS-IH (presence of family history and/or clinical signs and symptoms compatible with MPS-IH, i.e., phenotypic diagnosis based on clinical expertise), and/or homozygosity or compound heterozygosity for mutations associated with the severe phenotype. The recommendation that HSCT should be standard of care for MPS-IH patients is endorsed by the European Society for Blood and Marrow Transplantation and the American Society for Transplantation and Cellular Therapy.

Despite its established position in treatment algorithms, allogeneic-HSCT can result in alloreactive complications, including potentially fatal graft versus host disease, or GvHD, particularly when the degree of matching between graft donor and recipient is low. Additionally, although it may stabilize cognitive decline, life-threatening or severely debilitating cognitive, neurological, orthopedic, cardiac, respiratory and ophthalmic manifestations of MPS-IH have been reported during long-term post-HSCT follow-up.

Our solution, OTL-203 for treatment of MPS-I
Ex vivo autologous HSC gene therapy strategies aimed at correcting the genetic defect in patients could represent a significant improvement for the treatment of MPS-I, notably MPS-IH the most severe and prevalent phenotype with the highest unmet medical need, when compared to current treatments.

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

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

The therapeutic potential of this approach for addressing the extensive nervous system manifestations of MPS-IH is based on the contribution of HSCs to the turnover of CNS-resident microglia, demonstrated both in physiological and pathological conditions. Since microglia have been implicated in the pathogenesis of a number of neurodegenerative conditions, including LSDs. These cells should be considered a primary target cell type in therapeutic strategies for LSD with neurologic involvement such as MPS-IH. Moreover, compared to allogeneic transplantation, which is the current standard of care for MPS-IH treatment, the autologous nature of OTL-203 is associated with a significantly reduced transplant-related morbidity and mortality and avoids the risks of graft versus host disease.

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

Ongoing clinical trials
OTL-203 is currently being investigated in an ongoing, academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The study is a prospective, single dose, single center, non-randomized, open label study involving a single administration of OTL-203 in eight patients with a confirmed diagnosis of MPS-IH. The study is fully enrolled using a cryopreserved formulation of OTL-203.

The patients evaluated in this trial include pediatric MPS-IH patients from 14 to 35 months of age at the time of treatment and will be followed for at least five years post-treatment in the context of the proof of concept study and then continue to be evaluated in a long-term follow-up study.

In November 2021, we announced data published in the *New England Journal of Medicine* evaluating the safety and efficacy of OTL-203. For this publication's last follow up of all patients (range between 12 and 24 months), interim data supporting clinical proof-of-concept illustrated that treatment with OTL-203 was generally well-tolerated with a safety profile consistent with the selected conditioning regimen. IDUA antibodies present prior to gene therapy as a result of ERT were not seen in any patient within three months following treatment. In addition, ERT was discontinued at least three weeks prior to any patient receiving gene therapy treatment, and no patients had re-started ERT post-treatment.

In terms of biomarker data, treatment demonstrated rapid and sustained metabolic correction with all patients achieving supra-physiological IDUA expression in dried blood spot samples at 12 months (a primary efficacy endpoint). Associated with this, the results demonstrated increased IDUA expression in the CSF, with reduction of GAGs in CSF and normalization of GAG levels in urine.

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

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

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

Disease overviews

MPS-IIIA, also known as Sanfilippo syndrome type A, and MPS-IIIB, also known as Sanfilippo syndrome type B, are life-threatening metabolic diseases that cause accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within the first years after birth, MPS-IIIA and MPS-IIIB patients begin to experience progressive neurodevelopmental delay and decline, including speech delay and eventual loss of language, behavioral disturbances, and potentially severe dementia. Ultimately, most patients with MPS-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 or 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 commercialisation 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, completed enrollment in 2021 with the fifth patient treated in September 2021.

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

In terms of biomarker data, SGSH enzyme expression in leukocytes and CD15+ cells increased from below normal levels at baseline to supra-physiological levels at three months in all five patients. Furthermore, investigators reported that within three months, there was >90% reduction in urinary

GAGs (heparan sulfate) in all treated patients. Levels continue to decrease throughout the length of follow-up. CSF GAGs (heparan sulfate) decreased from baseline in the first three patients with available data.

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

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

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

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

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

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

Preclinical development of OTL-204
Preliminary *in vitro* data obtained in 2020 have demonstrated that human cell lines and mouse HSCs can be efficiently transduced to produce GRN. GRN is then secreted in the culture medium and can be taken up by other types of cells that do not produce GRN themselves.

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

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

Research program in ALS

Disease overview

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

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

Limitations of current therapies

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

Our solution, OTL-205 for treatment of ALS

OTL-205 is an *ex vivo* autologous gene therapy being developed to genetically modify microglia cells so that they have a much lower level of Nox2 and therefore produce less oxidative stress and less local inflammation. Microglia cells can be derived from HSCs. In our approach, HSCs are extracted from the patient, modified in the laboratory with the lentiviral vector and then infused back into the patient. These modified HSCs then migrate into the brain, where they become microglia cells replacing the diseased cells and reducing inflammation. This approach has the potential to improve symptoms and prolong survival in all ALS patients irrespective of their genetic mutations. OTL-205 is being developed in partnership with Professor Alessandra Biffi at the University of Padua in Italy. As part of the collaboration, we initiated a sponsored research agreement with the University of Padua and obtained an exclusive option with Boston Children's Hospital to develop and exclusively license the program.

Preclinical development of OTL-205

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

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

Immunological Disorders

Research program in NOD2-Crohn's Disease

Disease overview

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

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

Limitations of current therapies

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

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

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

Preclinical development of OTL-104

OTL-104 preclinical work has shown that restoration of NOD2 gene expression in murine and human stem cells can rescue a defective myeloid immune response to microbial peptides. NOD2 defective inflammatory functions in primary human myeloid cells can be restored by both lentiviral and gene editing approaches. Preclinical studies to evaluate the safety of this approach show that NOD2-LV

gene modification of human CD34+ stem cells does not affect HSC engraftment or immune subset development and differentiation following transplantation into NSG mice. Transplantation of NOD2-LV gene modified murine stem cells further demonstrates that HSC derived transgene+ cells can efficiently migrate and reconstitute the myeloid cell compartments of intestinal tissue.

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

Other programs

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

Blood disorders

Gene therapy for treatment of TDT

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

Future applications of our ex vivo autologous HSC gene therapy approach

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

Our regulatory strategy

The nature of our autologous gene therapy product candidates precludes the conduct of Phase 1 safety studies in healthy volunteers. Moreover, considering the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare indications with high unmet medical need, we believe our clinical programs will generally be eligible to proceed to registration based on a single pivotal study given the bioethical considerations regarding the conduct of randomized, double-blind and placebo-controlled clinical trials with gene therapies for such indications. Both the FDA and EMA provide expedited pathways for the development of drug product candidates for the treatment of rare diseases, particularly life-threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following one or more clinical trials in a limited patient population, following review of the trial's design, endpoints and clinical data by the applicable regulatory agencies. These determinations are based on the applicable regulatory agency's scientific judgement and these determinations may differ in the United States and the European Union.

In some cases applicable regulatory agency may require us to perform analytical studies or conduct additional clinical trials to support analytical comparability of drug product, for example by demonstrating comparability of drug product manufactured using HSCs derived from a patient's mobilized peripheral blood and drug product manufactured using HSCs derived from a patient's bone

marrow and/or comparability of drug product that has been cryopreserved and fresh drug product. For purposes of this Annual Report we refer to these clinical trials as supportive clinical trials. In addition, certain of our product candidates may be evaluated in clinical trials for which clinical data is not intended to be pooled with data from our registrational trials for purposes of a regulatory submission, but will be submitted to the applicable regulatory agencies for informational purposes. For purposes of this Annual Report we refer to these trials as additional clinical trials. In addition, in some cases patients may be ineligible for participation in our clinical trials and may receive treatment under a compassionate use program or an expanded access program. We expect that the available safety and efficacy results from all these trials would be included in any regulatory submission we may submit, and the applicable regulatory agency with respect to each clinical program will make a determination as to whether the available data is sufficient to support a regulatory submission.

Manufacturing

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

Global supply network with experienced CDMOs

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

Manufacturing efficiencies and scalability

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

Cryopreservation of our gene therapy programs

Cryopreservation of gene-modified cells is a key component of our strategy to deliver innovative, potentially curative gene therapies to patients worldwide. We have developed cryopreserved formulations of our OTL-200 and OTL-103 programs and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future submissions for marketing approval in the United States and Europe. Our programs in OTL-102, OTL-203 and OTL-201 have already started or will start with cryopreserved formulations. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

In the cryopreservation process, a patient's gene-modified HSCs are frozen at extremely low temperatures and then stored to allow quality control testing and release to be performed before

introducing the gene-modified cells back into the patient. Our cryopreserved formulations are expected to have shelf-lives of months to years, enabling us to potentially distribute our products and product candidates from a few centralized manufacturing facilities to geographically dispersed treatment sites. Our ability to ultimately distribute our product candidates globally will facilitate access of the therapies to patients and reduce the logistical burden on patients and their families.

Commercial operations

We have commercially launched Libmeldy (OTL-200) for the treatment of early-onset MLD following receipt of full, or standard, marketing approval from the European Commission in December 2020. We have substantially completed our build-out of our commercial operations in Europe with the goal of delivering Libmeldy to patients through qualified treatment centers in the UK, France, Germany, Italy and the Netherlands. In addition, we expect to leverage cross-border and treatment abroad reimbursement pathways in both Europe and markets such as the Middle East and Turkey through third-party strategic partners and distributors. Subject to approval of OTL-200 from the FDA, we plan to also put in place commercial operations and quality treatment centers in the U.S.

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

As part of the commercialisation process, we are engaged in discussions with stakeholders across the healthcare system, including public and private payors, patient advocates and organizations, and healthcare providers, to drive more timely patient identification through education, newborn screening, and diagnostic initiatives and to explore new payment models that we hope will enable broader patient access. We have initiated pilot studies for newborns in certain countries to screen for MLD and develop the necessary data package to enable universal newborn screening in various countries where we expect our products to be sold. Ultimately, we intend to utilize the commercial infrastructure that we are building to support the potential for multiple product launches, if approved, across multiple geographies. For many territories and countries, we may also elect to utilize strategic partners, distributors, or contract field-based teams to assist in the commercialisation of our products.

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

Intellectual property and barriers to entry

Our commercial success depends, in part, upon our ability to protect commercially important and proprietary aspects of our business, defend and enforce our intellectual property rights, preserve

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

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

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

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

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment to accommodate for administrative delays caused at the U.S. Patent and Trademark Office, or USPTO,

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

License agreements

GSK asset purchase and license agreement

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

Under the GSK Agreement, we are subject to certain obligations to develop and advance certain of the acquired product candidates. For example, we were required to use best endeavors to file an MAA for OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. In December 2020, we received full, or standard, marketing authorization for Libmeldy in the European Union as well as the United Kingdom, Iceland, Liechtenstein and Norway.

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

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. We will pay a mid-single-digit percentage royalty on the annual net sales of Strimvelis. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties

owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048.

We may terminate our development or commercialisation activities of any of the programs under the GSK Agreement upon the occurrence of an SAE, if we believe such program poses a safety risk to patients or in certain additional situations. GSK may require us to grant a third party a non-exclusive license under the intellectual property we have acquired from GSK under the GSK Agreement if we materially breach our obligations to use best endeavors or commercially reasonable efforts, as applicable, to develop and commercialise the acquired programs and fail to develop and implement a mutually agreeable plan to cure such material breach within a specified time period. The foregoing hypothetical license would only continue until such time as we cured our material breach, and we would be required to pay GSK all amounts we received from the third party in connection with such license.

Telethon-OSR research and development collaboration and license agreement

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

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicensable license under certain intellectual property rights to develop and commercialise *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 commercialise certain vectors and gene therapy products from disease-specific development programs for the treatment of WAS, MLD and TDT. At the time we entered into the novation agreement, GSK had completed development, launched and commercialised Strimvelis for ADA-SCID in the European Union, and had exercised its exclusive option to obtain exclusive licenses from Telethon-OSR to the WAS, MLD and TDT programs. We acquired Strimvelis and GSK's exclusive licenses relating to the ADA-SCID, WAS, MLD and TDT collaboration programs pursuant to the GSK Agreement and the deed of novation.

Under the R&D Agreement, Telethon-OSR is required to use commercially reasonable efforts to conduct each of the collaboration programs in accordance with development plans approved by a joint steering committee. With respect to those programs in relation to which our option has been exercised, we are required to use commercially reasonable efforts to develop, obtain regulatory approval, launch and promote in both the European Union and the United States all licensed products and to commercialise and manufacture such products at levels sufficient to meet commercial demands. We are required to use best efforts to renew the European Union marketing authorization for Strimvelis to enable patients to be treated at the San Raffaele hospital from all referring centers globally, as permitted by applicable law. We are responsible for the costs and activities associated with the continued development of Strimvelis and each program for which an option under the R&D Agreement is exercised.

As consideration for the licenses and options granted under the R&D Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are obligated to pay up to an aggregate of €31.0 million ($35.0 million at December 31, 2021) in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDT programs). Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves a certain threshold percentage of the market share.

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

Oxford BioMedica license and development agreement

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

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

As consideration for the licenses granted under the agreement, we issued 588,220 of our ordinary shares to Oxford BioMedica. We are also obligated to issue additional equity upon the achievement of certain milestones, pursuant to which we issued 150,826 ordinary shares upon the achievement of the first milestone in November 2017 and 150,826 ordinary shares were issued upon the achievement of further milestones in August 2018. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica. Additionally, we are obligated to pay low single-digit percentage royalties on net sales of licensed products until January 31, 2039. The foregoing royalties are reduced by a mid-double digit percentage in the case of compassionate use of a licensed product in a country until the first commercial sale following marketing authorization in such country. We are also required to pay a set monthly fee to Oxford BioMedica in the event we use a certain Oxford BioMedica system for generating stable cell lines.

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

Telethon-OSR license agreement

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

Competition

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

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

We are currently aware of the following competitive approaches among our products and clinical programs:

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

Passage Bio has a preclinical development program for MLD, and Affinia has a preclinical program for *in vivo* AAV gene therapy for MLD through lumbar puncture (LP) administration. We are also aware that Takeda is investigating an ERT for MLD with a biweekly intrathecal infusion, and Denali Therapeutics is at the preclinical stage of developing a recombinant ARSA enzyme engineered to cross the blood-brain barrier.

- **MPS-I**: The current standard of care for MPS-IH patients is HSCT before the age of 30 months. We are aware that REGENXBIO is developing an AAV-based gene therapy, which is in Phase I trials and to be delivered intracisternally. bluebird bio and Immusoft have both reported that they are developing *ex vivo* cell therapies in the preclinical stage. For MPS-I patients that are not suitable candidates for HSCT because they lack a suitable donor, were diagnosed later in life, or have a less severe subtype of MPS-I, the current standard of care for the treatment of MPS-I involves regular intravenous injections of laronidase (Aldurazyme), an ERT commercialised by BioMarin and Sanofi Genzyme. A formulation of laronidase for intrathecal administration is currently under evaluation. JCR Pharmaceuticals is developing an ERT, which is in Phase I trials. Denali Therapeutics has an ERT program in the discovery stage.
- **MPS-IIIA**: There are currently no effective disease modifying treatment options for patients with MPS-IIIA. We are aware of three gene therapy candidates in clinical development. Lysogene is developing an AAV gene therapy product administered through intracerebral injections, in a collaboration with Sarepta Therapeutics that is set to terminate in July 2022; Abeona Therapeutics is developing AAV gene therapy product administered intravenously; and Esteve is developing an AAV gene therapy administered through intracerebroventricular injection. Amicus Therapeutics is at the preclinical stage of developing an AAV gene therapy for MPS-IIIA. We are aware that JCR Pharmaceuticals and Denali Therapeutics each has a preclinical stage ERT program for MPS-IIIA.
- **GRN-FTD**: There are no approved disease modifying treatments for GRN-FTD. Each of Prevail Therapeutics (now owned by Eli Lilly & Company) and Passage Bio is developing in early-stage clinical trials an AAV gene therapy to be delivered intra-cisterna magna. Alector is developing a monoclonal antibody designed to increase levels of GRN in the brain in late-stage clinical trials, and Denali Therapeutics is developing a modified protein designed to penetrate across the blood-brain barrier at the preclinical stage in collaboration with Takeda.
- **ALS**: There are currently few approved treatment options for ALS, limited to riluzole and edaravone. Multiple companies are developing gene therapies for genetically defined populations of ALS. We are not aware of any companies developing therapies targeted to reduce expression of Nox2.
- **NOD2-Crohn's**: There are no approved treatment options specifically for the NOD-2 form of Crohn's disease, and many patients with Crohn's disease have uncontrolled symptoms despite treatment with standard of care, including multiple anti-inflammatory biologics and surgical interventions. We are not aware of any other treatments in development specifically for the NOD-2 form of Crohn's disease.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialise 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 commercialising any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. biological products development process

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

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, unless justified, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- approval of the protocol and related documentation by an independent institutional review board, or IRB, or ethics committee at each clinical trial site before each study may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a biologics license application, or BLA, for marketing approval that includes sufficient evidence of establishing the safety, purity, and potency of the proposed biological product for its intended indication, including from results of nonclinical testing and clinical trials;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with current good manufacturing practice, or cGMP, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or CGTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA in accordance with any applicable expedited programs or designations;
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

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

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

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

A sponsor may choose, but is not required, to conduct a foreign clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an

IND or application for marketing approval or licensing. In particular, such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The FDA must be able to validate the data through an onsite inspection, if deemed necessary by the FDA.

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

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

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

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

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

- *Phase 1*. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *Phase 2*. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

- *Phase 3*. Clinical trials are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for approval and product labeling.

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

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

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

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval.

Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as

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

U.S. review and approval processes

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

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

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

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the CGTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through appropriate screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. During the ongoing COVID-19 pandemic, restrictions preventing the conduct or completion of facility or clinical site inspections have led and may continue to lead to FDA deferred action on marketing applications or the issuance of complete response letters. To assure cGMP, CGTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

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

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

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

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, for products being considered for accelerated approval, the FDA generally requires, unless otherwise informed by the agency, that all advertising and promotional materials intended for dissemination or publication within 120 days of marketing approval be submitted to the agency for review during the pre-approval review period.

RMAT designation

As part of the 21st Century Cures Act, enacted in December 2016, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of RMAT, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. RMAT do not include those HCT/Ps regulated solely under section 361 of the PHS Act and 21 CFR Part 1271. This program is intended

to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. Like some of FDA's other expedited development programs, RMAT designation does not change the standards for approval but may help expedite the development or approval process.

Post-approval requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to cGMP. We currently rely, and may continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialise. 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 23 March 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the

reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

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

Additional regulation

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

U.S. Foreign Corrupt Practices Act

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

Government regulation outside of the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting,

advertising and other promotional practices involving biological products as well as authorization and approval of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Clinical trials regulation
Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials.

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

Drug review and approval
In the EU, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered

products. Gene therapy products deliver genes into the body that lead to a therapeutic, prophylactic or diagnostic effect. Libmeldy is authorized as a gene therapy product in the EU, and we anticipate that our gene therapy development products would also be regulated as ATMPs in the EU.

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

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

Data and marketing exclusivity

The EEA also provides opportunities for market exclusivity. Upon receiving marketing authorization in the EEA, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from referencing the innovator's preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization during a period of eight years from the date on which the reference product was first authorized in the EEA. During the additional two-year period of market exclusivity, a generic or biosimilar marketing

authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity period. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if an innovative medicinal product gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on a MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials. There is, however, no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may therefore not qualify for data exclusivity.

Orphan designation and exclusivity
Products with an orphan designation in the EU can receive ten years of market exclusivity, during which time "no similar medicinal product" for the same indication may be placed on the market. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. An orphan product can also obtain an additional two years of market exclusivity in the EU where an agreed pediatric investigation plan for pediatric studies has been complied with. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

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

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

Since 1 January 2021, a separate process for orphan designation has applied in Great Britain. There is now no pre-marketing authorization orphan designation (as there is in the EU) in Great Britain and the application for orphan designation will be reviewed by the MHRA at the time of an MAA for a UK or Great Britain MA. The criteria for orphan designation are the same as in the EU, save that they apply to Great Britain only (e.g., there must be no satisfactory method of diagnosis, prevention or treatment of the condition concerned in Great Britain, as opposed to the EU, and the prevalence of the condition must not be more than five in 10,000 persons in the EU).

Pediatric development

In the EU, companies developing a new medicinal product must agree upon a pediatric investigation plan, or PIP, with the EMA's Pediatric Committee, or PDCO, and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which marketing authorization is being sought. The MAA for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted by the PDCO of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization with the results of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six-month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) even where the trial results are negative. In the case of orphan medicinal products, a two-year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

PRIME Designation

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation, where the MAA will be made through the centralized procedure. Eligible products must target conditions for which 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 MAA assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the CHMP or CAT are appointed early in the PRIME scheme facilitating increased understanding of the product at EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

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

- The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.
- All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.
- All advertising and promotional activities for the product must be consistent with the approved SmPC and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the European Union. Although general requirements for advertising and promotion of medicinal products are established under European Union directives, the details are governed by regulations in each European Union Member State and can differ from one country to another.

Brexit and the Regulatory Framework in the UK
In June 2016, the electorate in the UK voted in favor of leaving the EU (commonly referred to as "Brexit"), and the UK formally left the EU on 31 January 2020. There was a transition period during which EU pharmaceutical laws continued to apply to the UK, which expired on 31 December 2020. However, the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since 1 January 2021 and has been formally applicable since 1 May 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore largely aligns with current EU regulations, however it is possible that these regimes will diverge in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation.

Other healthcare laws and compliance requirements
In the United States, our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs may have to comply with the anti-fraud

and abuse provisions of the Social Security Act, the false claims laws, the privacy and security provisions of the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, and similar state laws, each as amended, as applicable:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;
- the federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payers if they are deemed to "cause" the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure

of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;

- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective 1 January 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

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

We may also be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, or EEA, including personal health data, is subject to the General Data Protection Regulation 2016/679 (EU GDPR), which became effective on 25 May 2018. Further to Brexit on 31 January 2020 and the expiry of the subsequent transition period on 31 December 2020, the EU GDPR has been brought into UK law as the "UK GDPR". In the present document, references to "GDPR" are meant to include both the EU and the UK GDPR, unless specified. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines, imprisonment and/or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the U.S. government under the federal False Claims Act as well as under the false claims laws of several states.

Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, any of which could adversely affect our ability to operate our business and our financial results. In addition, our gene therapy programs for Strimvelis and Libmeldy were approved by the EMA in 2016 and 2020, respectively, and the approval and commercialisation of Strimvelis and Libmeldy subjects us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws. The approval and commercialisation of any of our other gene therapies outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

If any of the physicians or other healthcare providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business.

The risk of our being found in violation of these laws is increased by the fact that many of these laws have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain a robust system to comply with multiple jurisdictions with different compliance and reporting requirements increases the possibility that a healthcare company may violate one or more of the requirements. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial cost.

Healthcare reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or ACA, was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjected drug manufacturers to

new annual, nondeductible fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; expanded healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance; expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; expanded the entities eligible for discounts under the PHS Act's pharmaceutical pricing program, also known as the 340B Drug Pricing Program; created new requirements to report financial arrangements with physicians and teaching hospitals, commonly referred to as the Physician Payments Sunshine Act; created a new requirement to annually report the identity and quantity of drug samples that manufacturers and authorized distributors of record provide to physicians; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established the Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

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

Prior to the Biden administration, in October 2017, former President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. The former Trump administration concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until those appropriations are made. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on 25 October 2017. On 14 August 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 14 June 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 27 April 2020, the United States Supreme Court reversed the U.S. Court of Appeals for the Federal Circuit's decision and remanded the case to the U.S. Court of Federal Claims, concluding the government has an obligation to pay these risk corridor payments under the relevant formula. It is unclear what impact these rulings will have on our business.

In addition, CMS published a final rule that would give states greater flexibility as of 2020 in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect

of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

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

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

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under

Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On 10 March 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 1 January 2020. This final rule codified CMS's policy change that became effective 1 January 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 27 December 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 31 July 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 14 September 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), but was denied on 16 October 2020. Plaintiffs-appellees filed a petition for a writ of certiorari at the Supreme Court on 10 February 2021. On Friday 2 July 2021, the Supreme Court granted the petition. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any. While a number of these and other proposed measures will require authorization through additional legislation to become effective, Congress and has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, and review the relationship between pricing and manufacturer patient programs. At a federal level, President Biden signed an Executive Order on 9 July 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA

to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. FDA released such implementing regulations on 24 September 2020, which went into effect on 30 November 2020, providing guidance for states to build and submit importation plans for drugs from Canada. On 25 September 2020, CMS stated drugs imported by states under this rule will not be eligible for federal rebates under Section 1927 of the Social Security Act and manufacturers would not report these drugs for "best price" or Average Manufacturer Price purposes. Since these drugs are not considered covered outpatient drugs, CMS further stated it will not publish a National Average Drug Acquisition Cost for these drugs. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates. Further, on 20 November 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been 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. However, on 29 December 2021 CMS rescinded the Most Favored Nations rule. Additionally, on 30 November 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until 1 January 2026. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that they will continue to seek new legislative measures to control drug costs.

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

Coverage and reimbursement

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

not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development and manufacturing costs. Further, due to the COVID-19 pandemic, millions of individuals have lost or may lose employer-based insurance coverage, which may adversely affect our ability to commercialise 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)

Management closely monitors cash position and runway. As of 31 December 2021, we had cash, cash equivalents, marketable securities, and restricted cash of $224.4 million up from $196.2 million in 2020. Our research and development expenses are also closely monitored and have decreased from $93.7 million in 2020 to $87.0 million in 2021. In addition, we assess our performance through clinical and regulatory advancement of our programs. Following the approval of our lead program, OTL-200, by the European Union, the United Kingdom, Iceland, Liechtenstein and Norway under the

brand name Libmeldy for eligible patients with early-onset metachromatic leukodystrophy, or MLD, in December 2020, we initiated commercial launch activities in 2021. In July 2021, we announced a strategic collaboration with Pharming Group N.V. to research, develop, manufacture and commercialize OTL-105, an investigational ex vivo autologous HSC gene therapy for the treatment of hereditary angioedema, a life-threatening rare disorder that causes recurring swelling attacks in the face, throat, extremities and abdomen. We also completed the enrolment of five patients in a proof-of-concept trial for OTL-201 for MPS-IIIA; the fifth patient was treated in September 2021. Finally, in November 2021, we announced data published in the New England Journal of Medicine evaluating the safety and efficacy of OTL-203 for MPS-IH.

Employees and Human Capital Resources

As of 31 December 2021 we had 259 full-time employees (2020: 224). We have no collective bargaining agreements with our employees, and we have not experienced any work stoppages. We consider our relationship with our employees to be positive. We monitor employee engagement through an annual survey and develop a prioritized action plan on an annual basis to address any areas in need of attention. Our human capital objectives include, as applicable, identifying, recruiting, developing, retaining, and incentivizing our existing and prospective employees, as well as optimizing the overall employee experience. The principal purposes of our incentive plans are to attract, retain and motivate our employees. The granting of share-based compensation awards is designed to reward selected employees for long-term shareholder value creation and our cash-based performance bonus awards reward the achievement of annual performance goals. The health and safety of our employees, customers and communities are of primary concern. During the COVID-19 pandemic, we have taken significant steps to protect our workforce, including, but not limited to, working remotely and implementing social distancing protocols consistent with guidelines issued by federal, state and local laws.

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, and for any of our other product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. Before we submit our product candidates for marketing approval, the U.S. Food and Drug Administration or the European Medicines Agency may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.
- Interim data and *ad hoc* analyses are preliminary in nature. Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

- Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience, and we rely on third-party manufacturers that are often our single source of supply. We could experience manufacturing problems that result in delays in the development or commercialisation of our commercial products or our product candidates or otherwise harm our business.
- Libmeldy™, Strimvelis® and our product candidates and the process for administering Libmeldy, Strimvelis and our product candidates may cause serious or undesirable side effects or adverse events or have other properties that could delay or prevent regulatory approval, limit commercial potential or result in significant negative consequences for our company.
- We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.
- If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market, sell and gain reimbursement for Libmeldy and our product candidates that may be approved, we may be unable to generate product revenue.
- If the size and value of the market opportunities for our commercial products or product candidates are smaller than our estimates, or if we have difficulty in finding patients that meet eligibility requirements for Libmeldy, or any of our product candidates, if approved, our product revenues may be adversely affected and our business may suffer.
- We face significant competition in our industry and there can be no assurance that our commercial products or our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialise any of our products or product candidates.
- Business interruptions resulting from the ongoing COVID-19 pandemic have caused and may continue to cause a disruption to the development of our product candidates and adversely impact our business.
- We may not be able to protect our intellectual property rights throughout the world.
- We may become subject to claims that we are infringing certain third-party patents, for example, patents relating to lentiviral vectors, or other third-party intellectual property rights, any of which may prevent or delay our development and commercialisation efforts and have a material effect on our business.
- We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialise 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 2021 have 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".

	2021	2020
Estimated greenhouse gas emissions from purchased electricity, heat, steam, or cooling for our own use (tCO^2e)	64.6	230.5
Intensity ratio: Total greenhouse gas emissions per employee on the basis of a monthly average of 238 full-time equivalent employees (2020: 250)	0.27	0.9

We have used evidence and estimates derived from information 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 2021 as compared to 2020 as we remained a primarily remote workforce due to the COVID-19 pandemic and completed the exit of some of our facilities in the United States.

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 2021 and 2020 is as follows:

31 December 2021:

	Male	Female	Total
Company Directors	6	2	8
Executives/Vice Presidents	15	10	25
Other Employees	88	145	233
Total Employees	103	155	258

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

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 UK Statutory Strategic Report (page 19). 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 67) and "Diversity" (page 69) sections of this UK Statutory 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 UK Statutory Strategic Report (page 67).
– the impact of the Company's operations on the community and the environment;	Refer to the "Employees and Human Capital Resources" (page 67), "Diversity" (page 69), and "Information on Environmental Matters" (page 69) sections of this UK Statutory Strategic Report.

The board has had regard to the following matters:	More information
– 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 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 25 April 2022 and signed on behalf of the Board of Directors by:

Hubert Gaspar
Director

25 April 2022

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 2021. 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 UK Statutory Strategic Report, beginning on page 18 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 UK Statutory Strategic Report. Total consolidated research and development expense during the year was $87.0 million (2020: $93.7 million).

Results and dividends
The Company's consolidated financial results for the year are set out on page 121 of this Annual Report. For the year ended 2021 the Directors do not recommend the payment of a dividend (2020: nil).

Directors
The Directors of the Parent Company who held office during the year and up to the date of signing 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 13 to the consolidated financial statements. Share capital activity for the 2021 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 2021 (2020: nil).

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

Going Concern

At 31 December 2021 the Group held cash, cash equivalents, and marketable securities of $220.1 million, and the Company held cash, cash equivalents, and marketable securities of $183.8 million. The Directors have prepared a forecast through the end of 2023 and expect that cash, cash equivalents, and marketable securities on hand as of 31 December 2021, 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.

Employee Involvement

The Company has outlined key human capital disclosures in our Strategic Report on page 67 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 69 of this Annual Report.

Financial Risk Management

Credit and Interest Rate Risk

As of 31 December 2021, we had cash, cash equivalents, marketable securities, and restricted cash of $224.4 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying UK and U.S. bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We have borrowed $33.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 5.95% plus LIBOR. As of 31 December 2021, the carrying value of the term loans under the credit facility was $32.9 million.

In 2017, the United Kingdom's Financial Conduct Authority announced that after 2021 it would no longer compel banks to submit the rates required to calculate the London Interbank Offered Rate (LIBOR) and other interbank offered rates, which have been widely used as reference rates for various securities and financial contracts, including loans, debt and derivatives. This announcement indicates that the continuation of LIBOR on the current basis is not guaranteed after 2021. Regulators in the U.S. and other jurisdictions have been working to replace these rates with alternative reference interest rates that are supported by transactions in liquid and observable markets, such as the Secured Overnight Financing Rate (SOFR). Currently, our credit facilities reference LIBOR-based rates. The discontinuation of LIBOR will require these arrangements to be modified in order to replace LIBOR with an alternative reference interest rate, which could impact our cost of funds. Our credit facilities include a provision for the determination of a successor LIBOR rate.

Liquidity Risk

From our inception through 31 December 2021, we have not generated significant revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We acquired our commercial product Strimvelis and the program that is now Libmeldy from GSK in April 2018, and our product candidates are in various phases of preclinical and clinical development. In December 2020, the European Commission granted standard marketing authorization for Libmeldy. We expect to launch Libmeldy in Europe and generate product sales in early 2022. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our IPO and follow-on offering, proceeds from the sale of ordinary shares in our private placement, proceeds from the sale of convertible preferred shares, proceeds associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program, reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., our Original Credit Facility and our Amended Credit Facility.

On 27 February 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 31 December 2021, we have not sold any shares under the Sales Agreement. On 24 March 2022, we delivered written notice to Cowen to terminate the Sales Agreement, effective as of 30 March 2022, pursuant to Section 11(b) thereof. Prior to termination, we had not sold any ADSs pursuant to the Sales Agreement. As a result of the termination of the Sales Agreement, we will not offer or sell any ADSs under the Sales Agreement.

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

Foreign exchange risk

The Company is exposed to foreign currency exchange risk because it currently operates in the United Kingdom and the United States. The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the ultimate parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises finance and expends cash in U.S. dollars, and expects to continue to do so in the future. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency of the relevant entity at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net income/(loss) for the respective periods. We recorded realized and unrealized foreign currency losses of $1.2 million and gains of $3.4 million for the years ended 31 December 2021 and 2020. These foreign currency transaction gains and losses are included in other (expense)/income in our consolidated statements of operations and comprehensive loss.

Assets and liabilities have been translated at the exchange rates at the balance sheet 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

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
Orchard Therapeutics (Switzerland) GmbH	Switzerland

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:

Hubert Gaspar
Director

25 April 2022

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 proposed 2022 Directors' Remuneration Policy and the Directors' Remuneration Report for the year ended 31 December 2021 (the "Remuneration Report").

The Company's Remuneration Report, will be subject to an advisory vote at the forthcoming Annual General Meeting on 7 June 2022 (the "AGM") and our 2022 Directors' Remuneration Policy subject to a binding vote and, if approved, valid for a maximum of three years from that date.

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.

With these various factors in mind, myself and the Compensation Committee believe that the overall structure of our Directors' Remuneration Policy remains appropriate to attract, retain and motivate directors to execute the Company's strategy. We recognize the evolving best practices in remuneration governance, and we have incorporated the following into our proposed Policy beginning this year: (i) shareholding requirements for Executive Directors and, (ii) recovery provisions (malus and clawback) on to all incentive compensation. We believe these are important updates to a Policy which serves our shareholders well in our competitive landscape in the global biotechnology sector.

Key remuneration decisions for 2021

The Committee and I were mindful of the Company's overall financial position and the Company's share price performance during the year. We acknowledge and celebrate the many achievements made by all of our colleagues at Orchard while ensuring the broader context of the Company is considered when making remuneration decisions.

In January 2021, the Committee welcomed, and endorsed a proposal from the CEO, that he would not receive any increase in base salary during 2021. This was consistent with the remainder of the leadership team at that time. His target bonus also remained at 60% salary. As CEO, we granted Dr. Gaspar the option to purchase 850,000 shares, effective February 1, 2021 – the level of this award benchmarked against our industry peers.

2021 Annual Bonus

Orchard's annual bonus is based on stated corporate objectives set by the Board and the Compensation Committee at the beginning of the year. For 2021 this was made up of a combination of objectives contributing to the foundation of a sustainable commercial business, advancing our portfolio towards key clinical and regulatory milestones, and maintaining a performance-driven culture both internally and with our partners.

For the CEO, executive team and consistent for all employees, the Committee determined a corporate score of 60% of target. This is reflective of the Company as a whole making considerable strides towards all of our stated objectives while also acknowledging that a number of key objectives fell short of expectations due to either internal or external factors. The Committee's decision is taken in the context of the broader financial position of the Company, the share price performance during the year, and the competition for talent in the global biotechnology sector.

Remuneration for 2022

There are no substantial changes to our approach to executive compensation for 2022.

Consistent with our pay for performance philosophy, we intend to grant Dr. Gaspar an annual award of share options in 2022. In prior years all options have been awarded at market value. For 2022, and reflecting the Company's share price performance, we propose to grant half of the 2022 award in premium-priced options - options with an exercise price above the stock price on the date of grant. This installs a further hurdle before any of Dr. Gaspar's long-term incentive has any intrinsic value and further aligns our compensation approach with the shareholder experience.

Changes to the Board

Jon Ellis did not seek re-election to the Board at the 2021 AGM and ceased to be a Director on 16 June 2021. Dr. Ellis received no remuneration from Orchard and we thank him for his services to the Company.

Conclusion

The Committee believes that the Directors' Remuneration Policy has been implemented fairly and consistently, as described in this report. With the governance updates we are proposing, we are confident 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

25 April 2022

Remuneration Policy

The following section sets out our Directors' Remuneration Policy (the "Policy") which will be put to a binding shareholder vote at the annual general meeting on 7 June 2022. If approved, it will be effective from that date.

The current Directors' Remuneration Policy was approved by shareholders in June 2019, therefore a new policy is being presented under the standard three-year renewal cycle. The current policy received strong shareholder support, as has the implementation of the policy in the annual voting. The Compensation Committee is of the view that the overall structure continues to be appropriate for a company in Orchard's position reflecting the competitive environment for talent while including developments in market and governance best practices.

Key considerations when determining the Remuneration Policy

The Policy is 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.

Key changes to the Remuneration Policy

The Committee maintains that the overall structure of remuneration is appropriate and no fundamental structural changes are proposed. The Committee does acknowledge that there are developments in market and best practices which include:

- Introduction of share ownership requirements for Executive Directors – intends to ensure long-term alignment between our Executive Directors and shareholders.
- Introduction of recovery provisions (malus and clawback) – provides mitigation against payment for failure and ensures that all future incentive-based compensation in subject to recovery.
- The retainer arrangements for Non-Executive Directors will include the flexibility for Directors to elect a portion, or all, of their fees as either cash or in equity equivalents. This is common practice in the US and is included to ensure our Director compensation arrangements are competitive within our sector landscape.

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. 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. Benefits may also include payment by the Company of any stamp duty arising in respect of the settlement of equity incentives.	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.
Retirement benefits			
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. 6% is the contribution rate provided to all UK employees.	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. In exceptional circumstances, the Committee may add further performance measures and milestones during the year.	The target bonus opportunity for Executive Directors is up to 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 2022, 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. Any exceptional bonuses would operate within the overall annual maximum 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
Long-term incentives At the date of this Policy, long-term incentives are normally granted under the 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 made in relation to appointment generally vest 25% after one year, and monthly thereafter for 36 months. Currently, time-based RSUs normally vest in equal installments annually over a total period of no less than three-years. Performance Share Units ("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
All employee share schemes			
Encourages employee share ownership and therefore increases alignment with shareholders. Executive Directors will be eligible to participate in any all-employee share scheme.	The Company currently operates an Employee Share Purchase Plan ("ESPP") 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. The Company may adopt equivalent arrangements in any jurisdiction in order to comply with local requirements.	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. At a Directors' election, cash retainers may be delivered as an equivalent number of share options – calculated at fair value on the date of grant - vesting quarterly over a one-year period. 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.

Shareholding guidelines

Executive Directors are expected to build up and maintain, a shareholding equivalent to a multiple their respective base salary. For the Chief Executive Officer, this multiple is equal to two-times their base salary and for any other Executive Director, one-times base salary. Executive Directors will have five years from either the adoption of the policy or their appointment to the Board, whichever is later, to achieve the target level of share ownership.

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.

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.

Recovery Provisions (malus and clawback)

Prior to vesting, the Compensation Committee may reduce or cancel any awards granted under the Company's 2018 SOIP, or impose additional conditions on awards in circumstances the Compensation Committees deems appropriate ('malus'). Such circumstances may include: a serious misstatement of the Group's audited financial results; a serious miscalculation of any relevant performance measure; a serious failure of risk management or regulatory compliance by a relevant entity; serious reputational damage to the Group; the participant's material misconduct, or a material corporate failure.

In addition, for cash bonus and SOIP awards the Compensation Committee may also apply malus and/or clawback in certain extreme circumstances (including those listed above) for up to two years following the determination of the relevant performance outcome of vesting of the award.

Prior to applying malus or clawback, the Compensation Committee will take into account all relevant factors (including, where a serious failure of risk management or regulatory compliance or serious reputational damage has occurred, the degree of involvement of the employee in that failure or damage in question and the employee's level of responsibility) in deciding whether, and to what extent, it is reasonable to operate malus and/or clawback. The Compensation Committee is satisfied that the above provisions provide robust safeguards against inappropriate payment of incentive awards.

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 and has formal responsibility for human capital measures across the Company with a particular focus on diversity and inclusion activities. 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 any all employee share scheme (for example, 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[1]	Chief Executive Officer	2 January 2018	6 months either party

1 Hubert (Bobby) Gaspar.

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.

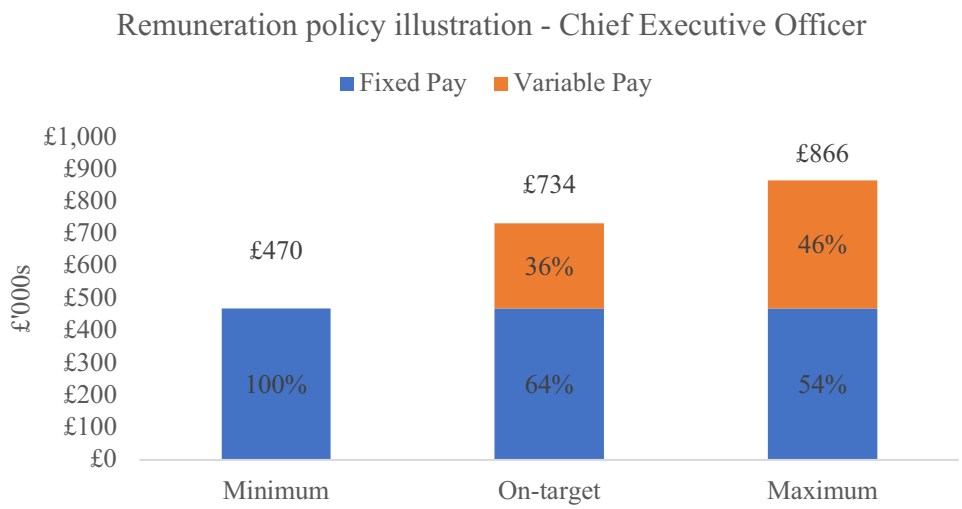
The dates of appointment of each of the Non-Executive Directors serving at 31 December 2021 are summarised in the table below. Dates prior to our incorporation in August 2018 as Orchard Rx Limited (now known as Orchard Therapeutics plc) are for Non-Executive Directors who served on the board of our predecessor company, Orchard Therapeutics Limited (now known as Orchard Therapeutics (Europe) Limited).

Non-Executive Directors	Date of contract or date of appointment	Service at 31.12.21
Joanne Beck	1 July 2018	3 years 6 months
Marc Dunoyer	6 June 2018	3 years 7 months
James Geraghty	4 June 2018	3 years 7 months
Charles Rowland	1 June 2018	3 years 7 months
Alicia Secor	7 December 2018	3 years 1 month
John Curnutte	30 August 2019	2 years 4 months
Steven Altschuler	3 February 2020	1 year 11 months

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.

Illustration of remuneration policy

The remuneration arrangements are designed to ensure that a significant proportion of pay is dependent on the Company's performance. The Compensation Committee considers the level of remuneration that may be received under different performance outcomes to ensure that this is appropriate in the context of the success of the Company. The chart below provides illustrative values of the annual compensation package for the Chief Executive Officer in 2022 under three assumed performance scenarios. This chart below is for illustrative purposes only and actual outcomes may differ from those shown. The variable remuneration in the charts below only include annual bonus opportunity. Executive Directors typically receive an annual award of market value options, the intrinsic value of which is zero at grant, and is therefore only included in the share price appreciation element.



	Assumed performance	Assumptions
Fixed pay	All performance scenarios	Consists of fixed pay including base salary, benefits and retirement benefits. – Base salary – as effective 1 January 2022 – Benefits – using 2021 values – Retirement benefits – 6% salary
Variable pay	Minimum	– No pay-out on annual bonus
	On-target	– CEO target bonus for 2022 = 60% salary
	Maximum performance	– Maximum bonus pay-out of annual bonus, at 1.5x target i.e. 90% salary
Share price appreciation	Impact of 50% Share-price appreciation	– Orchard typically awards long-term incentives to Executive Directors in the form of share options. – The number of share options granted to the CEO in 2021 and 2022 is 850,000 share options. – For illustrative purposes, were 850,000 share options granted at market value using closing price on 31 December 2021- $1.32, a 50% appreciation in the share price would result in a gain of $561,000.

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, The Companies (Directors' Remuneration Policy and Directors' Remuneration Report) Regulations 2019 ("the 2019 regulations") 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 7 June 2022.

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 2021

	Attendance
Charles Rowland	7 of 7
Joanne Beck	7 of 7
Alicia Secor	7 of 7

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 2021, Aon assisted the Committee and kept the Committee up to date on remuneration trends and regulations. During the 2021 financial year, fees charged by Aon for advice provided to the Committee amounted to $131,226 (2020: $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;
- preparing any report on executive remuneration required by the rules and regulations of the U.S. 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. During 2021, the Committee's remit was extended to oversee the Company's policies and strategies relating to culture and human capital management, including diversity and inclusion.

Statement of shareholder voting at 2021 AGM

At last year's AGM held on 16 June 2021, 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	94.9%	62,998,348	5.0%	3,299,947	0.1%	61,446

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 2021 (audited)

The total remuneration of the individual Directors who served in the year ended 31 December 2021, 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[3] $000	Bonus $000	SOIP[4] $000	PSUs[5] $000	Total remun-eration $000	Total fixed	Total variable
Executive Directors										
Bobby Gaspar	2021	605.1	3.2	27.2	217.8	–	–	853.4	635.5	217.8
	2020	542.5	6.6	–	169.9	–	44.8	763.8	549.1	214.7

		Base salary /fees $000	Benefits[2] $000	Pension $000	Bonus $000	SOIP[3] $000	PSUs[4] $000	Total remun-eration $000	Total fixed	Total variable
Non-Executive Directors										
Steven Altschuler[6]	2021	51.9	–	–	–	–	–	51.9	51.9	–
	2020	47.2	–	–	–	–	–	47.2	47.2	–
Joanne Beck	2021	59.4	–	–	–	–	–	59.4	59.4	–
	2020	58.0	–	–	–	–	–	58.0	58.0	–
John Curnutte	2021	63.7	–	–	–	–	–	63.7	63.7	–
	2020	60.5	–	–	–	–	–	60.5	60.5	–
Marc Dunoyer	2021	59.1	–	–	–	–	–	59.1	59.1	–
	2020	59.5	–	–	–	–	–	59.5	59.5	–
Jon Ellis[7]	2021	–	–	–	–	–	–	–	0.0	–
	2020	–	–	–	–	–	–	–	0.0	–
James Geraghty	2021	95.1	–	–	–	–	–	95.1	95.1	–
	2020	95.8	–	–	–	–	–	95.8	95.8	–
Charles Rowland	2021	78.1	–	–	–	–	–	78.1	78.1	–
	2020	78.7	–	–	–	–	–	78.7	78.7	–
Alicia Secor[8]	2021	72.1	–	–	–	–	–	72.1	72.1	–
	2020	53.0	–	–	–	–	–	53.0	53.0	–
Total	2021	1084.6	3.2	27.2	217.8	–	–	1332.8	1115.0	217.8
	2020	995.2	6.6	0.0	169.9	–	44.8	1216.5	1001.8	214.7

1. Dr Gaspar's salary is £440,000 per annum. 2021 figures are converted at a 12-month average rate for 2021 of GBP 1 = USD 1.3753. 2020 figures are converted at a 12-month average rate of GBP 1 = USD 1.2871.
2. For Executive Directors, included private health insurance, long term disability, critical illness and death in service benefits.
3. Effective 1 April 2021, Dr. Gaspar began receiving a cash allowance in lieu of the Company's pension contribution equal to 6% of his salary. Dr. Gaspar received no pension benefits from the Company before this date.
4. 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.
5. 6,250 PSUs vested for Dr. Gaspar 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.
6. Steven Altschuler joined the Board of Directors on 3 February 2020.

7. Jon Ellis did not stand for re-election at the 2021 AGM and left the Board on 16 June 2021. He received no remuneration for his services to the Board of Directors.
8. Alicia Secor received a one-time retrospective payment of $11,250 in April 2021 for prior services to the Nomination and Governance Committee which had previously not been paid.

2021 Annual bonus

During a series of meetings between December 2021 and February 2022, the Compensation Committee evaluated achievement of the 2021 corporate objectives and each Executive Director's individual performance.

The Compensation Committee reviewed the corporate goals, below, and based on the results approved a 60% achievement level of the 2021 corporate objectives.

Key achievements against agreed goals were as follows:

Build a foundation for a sustainable commercial business – A key element of Orchard's commercial model is expanding newborn screening programs for patient identification. During 2021, studies were established in US and Europe.

Important technology transfers to a U.S. CDMO were initiated and we advanced certain lentiviral vector manufacturing technology by establishing a stable cell line research bank which could eventually lead to a reduction in costs of product manufacturing. The manufacturing platform strategy was reviewed by our board of directors during 2021 and designed to achieve robust, reproducible and at-scale processes, another foundational element of our future commercial business.

We have also established internal process development labs in London to continue to enhance our viral vector and drug product manufacturing processes.

Advance our portfolio to key milestones – Interim clinical data was presented at medical conferences for OTL-203 (MPS-I) and OTL-201 (MPS-IIIA) that supports further advancement of our clinical programs in those indications. The data was presented for both programs at the WORLD medical meeting in February 2021. In addition, pre-clinical data in two research programs (e.g. FTD and Crohn's disease) that supported further development activities was also presented during 2021.

Maintain a performance-driven culture internally and with partners – Importantly, we completed a financing during 2021 with gross proceeds totaling $150 million, which extended our cash runway and executed a partnership with Pharming Group, which provided additional validation to the HSC gene therapy platform. Strimvelis was also returned to the European market following a favorable risk/benefit determination by regulatory bodies.

Internally, we completed the initial phase of our global diversity & inclusion initiative. This resulted in significant employee participation and engagement to support a strong culture and employee retention.

Additional achievements and considerations
Further to the corporate goals, a number of additional achievements are considered noteworthy for the company's performance during 2021. In terms of our pipeline

– we completed the enrollment in the OTL-201 (MPS-IIIA) proof-of-concept clinical trial;
– initiated new discovery projects and work on vectorizing antibodies, including the presentation of the scientific basis for these programs at a September R&D Day with investors and analysts;

– re-initiated patient recruitment for OTL-102 (X-CGD); and
– received EU Orphan Drug Designation for two new pre-clinical programs in our pipeline.

Our scientific activities were recognised with the publication of OTL-203 (MPS-I) clinical data and OTL-101 (ADA-SCID) clinical data in the New England Journal of Medicine and an integrated manuscript of OTL-200 (MLD) was accepted to Lancet. We also presented OTL-203 (MPS-I) clinical data during the Presidential Symposia at EHA 2021. In total, 46 posters or presentations covering our portfolio were made at medical meetings and congresses in 2021.

From a commercial perspective, launch activities are ongoing for Libmeldy with the first commercial price established in Germany and market access progress in France, UK and Italy.

Financially, we were able to refinance our credit facility allowing for increased borrowing capacity and a lower overall cost of capital.

The Committee also notes the successful changes to the Company's executive team including the additional capabilities of Nicoletta Loggia as Chief Technical Officer and Fulvio Mavilio as Chief Scientific Officer.

The achievements above contribute to the performance score of 60%.

Annual Bonus (audited)
A Corporate Performance Score of 60% corresponds to a bonus outcome equivalent to 60% of target for the CEO. This equates to a 2021 bonus payment equal to 36% of base salary.

The Committee notes that the same performance score has been applied consistently to all executives and employees across the Company.

Executive Director	Base salary ($)	Target Annual Cash Bonus (% of salary)	Corporate performance	Cash payment % salary	Cash outcome ($)
Bobby Gaspar	$605,114	60%	60%	36%	$217,841

1 Dr. Gaspar's base salary and bonus are paid in GBP (£) and awards have been translated into USD at a rate of GBP 1 = USD 1.3753, which was the average rate during 2021. The salary basis for the bonus was Dr Gaspar's salary as CEO, £440,000.

Share Option Incentive Plan

Awards granted to Executive Directors in 2021 (audited)

During 2021, Dr Gaspar received two equity awards:

– an annual equity award of share options; and

– an award of share options delivered in lieu of 50% of the 2020 annual bonus. The number of shares covered under this award was calculated using the grant date fair value. The delivery of a portion of the 2020 annual bonus was consistent with all members of the company's leadership team and the cash saving made by the Company as a result of this decision was used as additional funding to the available employee bonus pool.

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 31.12.21)	Exercised	Value realized at exercise or vesting	Un-vested
Bobby Gaspar	FMV Options	1 Feb 2021	850,000	$5.98	$5,083.0	$3,295.0	31/1/2031	(1)	177,083	nil	n/a	672,917
	FMV Options	1 Feb 2021	55,006	$5.98	$328.9	$209.7	31/1/2031	(2)	45,838	nil	n/a	9,168

* 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 vesting commencement date of 1 February 2021.

(2) The options vest, and become exercisable, over a one-year period on a monthly basis commencing upon the one-month anniversary of the vesting commencement date of 1 February 2021.

PSUs Vesting in the period

On 16 January 2019, Dr Gaspar had been granted 18,750 Performance Share Units subject to performance conditions.

On 17 December 2020, the Company received full marketing 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, one-third 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 were subject to additional performance conditions.

These additional performance conditions related to share price performance and clinical and regulatory milestones in relation to OTL-101 and OTL-103. Of the four performance conditions attributed to the PSU award, each had a 1/3rd weighting, with three of the four required for full vesting. Across these four, only the milestone relating to MLD was achieved. As none of the further conditions were met before 31 December 2021 the remainder of Dr. Gaspar's award – 12,500 shares – lapsed in full.

Awards granted to Non-Executive directors between 1 January 2021 and 31 December 2021 (audited)

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

Non-Executive Directors	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*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000
Joanne Beck	FMV Options*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000
Marc Dunoyer	FMV Options*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000
James Geraghty	FMV Options*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000
Charles Rowland	FMV Options*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000
Alicia Secor	FMV Options*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000
John Curnutte	FMV Options*	16-Jun-21	40,000	$4.79	$191,600	$121,592	15-Jun-31	(1)	nil	nil	nil	40,000

* 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.

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 2021 (together with interests held by his or her connected persons) are set out in the table below.

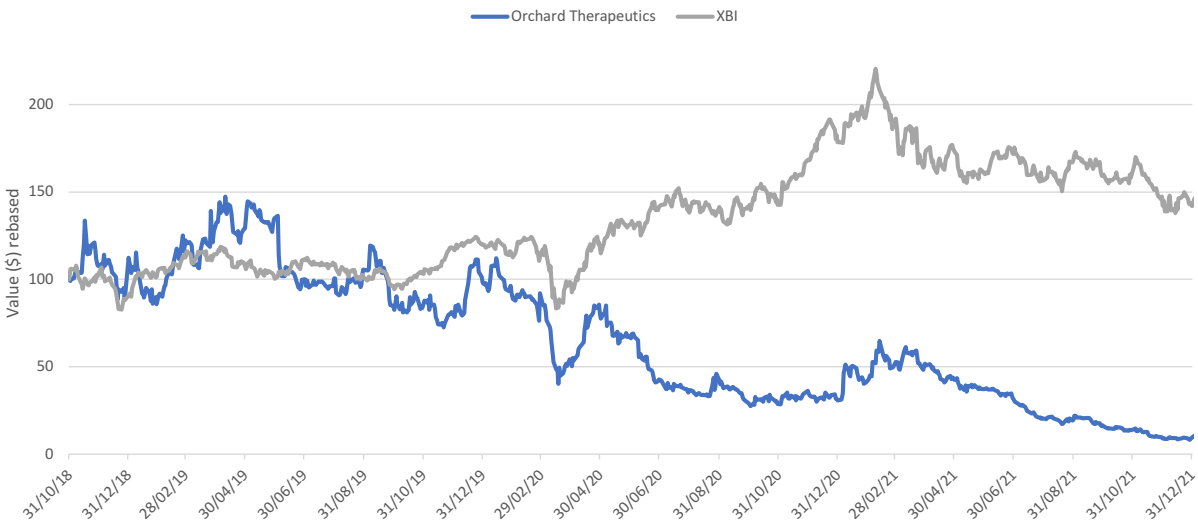
For 2021, Orchard Therapeutics did not operate any formal shareholding guidelines for Directors' shareholding requirements. From 2022 onwards, Executive Directors will be expected to build up and maintain a shareholding with a value relative to their salaries. For the CEO, this guideline is 200% of salary and for other Executive Directors, 100% salary. Executive Directors will be expected to exceed this guideline within 5 years of appointment or the implementation of this requirement.

		Shares		Share Options		
	Beneficially owned shares as at 31/12/21	Unvested without performance conditions	Unvested with performance conditions	Vested but unexercised	Unvested without performance conditions	Unvested with performance conditions
Executive Directors						
Bobby Gaspar	355,158	–	–	1,194,767	1,189,541	–
Non-Executive Directors						
Joanne Beck	9,294	–	–	150,030	40,000	–
John Curnutte	–	–	–	73,833	51,167	–
Marc Dunoyer	37,179	–	–	150,030	40,000	–
Jon Ellis[1]	–	–	–	–	–	–
James Geraghty	44,391	–	–	390,120	40,000	–
Charles Rowland	12,294	–	–	150,030	40,000	–
Alicia Secor	–	–	–	120,000	40,000	–
Steven Altschuler	–	–	–	65,555	59,445	–

1. Jon Ellis left the Board on 16 June 2021.

Performance graph and table

The chart below shows the Company's Total Shareholder Return (TSR) performance compared with that of the SPDR S&P Biotech Index (XBI) over the period from the date of the Company's admission to 31 December 2021. The XBI Index has been chosen as an appropriate comparator as a broad index comprising of small and mid-cap biotechnology companies. 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 2021, 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 XBI on the same date.

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	2021
Total remuneration ($000)[1]	$555	$1,016	$764	$853
Actual bonus (% of the maximum)	N/A	44%*	37.5%*	22.5%*
SOIP vesting (% of the maximum) **	N/A	N/A	N/A	N/A

1 For 2018 and 2019, these figures are for Orchard's previous CEO Mark Rothera and for 2020 and 2021 the full-year remuneration for Dr. Gaspar.

* Calculated as the bonus earned in the year by Dr. Gaspar 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 total operating expenses. Total operating expenses is a combined total of R&D and selling, general & administrative expenses before any deduction for any research and development tax credits recognised in the year. This is chosen as an appropriate measure of the Company's major year-on-year expenditure. It is considered to be a more complete representation of our operations compared to R&D expenses which had been used in prior years.

	2020	2021	% change
Total operating expenses	$181,866	$157,850	-13.2%
Total employee pay expenditure ($'000)[1]	$87,091	$73,704	-15.4%

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 $22,536 and $27,962k in non-cash share-based compensation expense for 2021 and 2020 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 2021.

	Change in pay between 31 December 2020 and 31 December 2021			Change in pay between 31 December 2019 and 31 December 2020		
	Base salary/ fee change	Bonus change	Benefit change	Base salary/ fee change	Bonus change	Benefit change
Executive Directors						
Bobby Gaspar[1]	12%	28%[2]	361%[3]	57.7%	-54%	0%
Non-Executive Directors[4]						
Joanne Beck	2%	n/a	n/a	41.4%	n/a	n/a
John Curnutte[5]	5%	n/a	n/a	278.0%	n/a	n/a
Marc Dunoyer	-1%	n/a	n/a	26.5%	n/a	n/a
Jon Ellis[6]	n/a	n/a	n/a	n/a	n/a	n/a
James Geraghty	-1%	n/a	n/a	15.0%	n/a	n/a
Charles Rowland	-1%	n/a	n/a	31.1%	n/a	n/a
Alicia Secor[7]	36%	n/a	n/a	23.0%	n/a	n/a
Steven Altschuler[8]	10%	n/a	n/a	n/a	n/a	n/a
Average employee[9]	n/a	n/a	n/a	n/a	n/a	n/a

Please note that all figures are impacted by exchange rate fluctuation between the currency in which the Board is paid, GBP, and our reporting currency, USD.

1 Dr. Gaspar did not receive a salary increase in 2021 for his services as CEO. The increases represented here corresponds to a salary increase upon promotion to CEO during 2020. This figure is also impacted by exchange rate fluctuations
2 The 2020 bonus (paid in February 2021) figure represents the cash amount paid only. Dr. Gaspar received share options with a fair value equal to 50% of the 2020 annual bonus in lieu of cash.
3 Dr. Gaspar's increase relates to a cash allowance in lieu of pension contribution effective 1 April 2021 which he had not received prior to that date.
4 None of the Non-Executive Directors are eligible for an annual bonus and none claimed any benefits during the year.
5 John Curnutte joined the Board in 2019 and the remuneration received in 2019 was not a full annual amount.
6 Jon Ellis did not receive any remuneration for his services to the Board and left the Board on 16 June 2021.
7 Alicia Secor receive a one-off retrospective payment of $11,250 in April 2021 for prior services to the Nomination and Governance Committee which has previously not been paid. Her fees for services to the Board were not increased during 2021.
8 Steven Altschuler joined the Board during 2020 and therefore no comparative information is shown.
9 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 2022

Annual base salary

On March 1 2022 Dr. Gaspar's salary was increased by 5%. This increase is in line with salary increases awarded to all employees at the Company who are eligible for a 2022 salary review.

	Base salary 2021	Base salary 2022	% change
Bobby Gaspar, Chief Executive Officer,	£440,000	£462,000	5%

Benefits and pension

In 2022, 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 rate for the rest of the workforce.

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).

These 2022 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.

Within the overall maximum annual bonus provision in the Directors' Remuneration Policy – currently 160% of salary per annum - the Committee reserves the right to provide an additional milestone-based bonus. This would only be applied in circumstances deemed appropriate to focus on and incentivize key fundamental objectives to the Company. Such an award would only be made to Executive Directors if equivalent incentives are provided to a significant proportion of, if not all, employees of the Company. In such circumstances, full details including performance conditions would be provided in the Directors' Remuneration Report for the relevant financial year.

Share Option Incentive Plan (SOIP)

Annual award of share options

In 2022, as part of the annual compensation package, the CEO will be granted no more than 850,000 share options in the Company at the same time as all eligible employees. At the date of this report, the Committee notes that these options have not been granted.

The Committee recognizes that the Company's share price has declined significantly and for that reason – half of the award – on a grant date fair value basis – will be granted as premium-priced share options. These premium priced options will have an exercise price set at 25% higher than the closing price of the Company's ADSs on the Nasdaq Global Select Market on the date of grant. Consequently, approximately half of the CEO's 2022 share option award will have no intrinsic value until the share price increases by at least 25%. The Committee believes that this further aligns the CEO with the shareholders of the Company considering recent share price performance and implementing an additional performance hurdle reinforces our pay for performance principle.

The overall maximum number of options that will be awarded is equal to the number of share options granted as an annual award made in 2021.

Executive Director	Form of Award	Anticipated Date of Grant	Maximum Shares Covered	Exercise Price	Vest Terms
Bobby Gaspar	Combination of FMV options and premium-priced share options	1 June 2022	850,000	On a fair value basis 50% of the award will be granted as market value options. The remaining 50% to be granted with an exercise price at a 25% premium to the closing price on the date of grant.	(1)

(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 not subject to any further performance conditions.

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, including the full details of the award described for Dr. Gaspar, will be disclosed in the relevant Directors' Remuneration Report.

Non-Executive Directors' fees for 2022

Non-Executive Directors are eligible to receive the following cash compensation annually. The cash fees remain unchanged for 2022.

	2022 Fee in $'000	2021 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 was effective 1 April 2021.

The Company provides an initial, one-time equity award of 92,000 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 46,000 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.

From 2022, and subject to shareholder approval, our Directors' Remuneration Policy will allow Non-Executive Directors the provision to elect to receive fees as market value share options with an equivalent value calculated as the fair value on the date of grant.

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

Each Non-Executive Director will also be entitled to reimbursement of reasonable expenses and reimbursement of up to $5,000 (2020: $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

25 April 2022

ORCHARD THERAPEUTICS PLC
PARENT COMPANY FINANCIAL STATEMENTS
FOR THE YEAR ENDED 31 December 2021

Registered Number: 11494381

Parent Company Balance Sheet

as at 31 December 2021

	NOTE	2021 $'000	2020 $'000
FIXED ASSETS			
Investments	2	–	279,625
CURRENT ASSETS			
Debtors	3	15,894	36,528
Prepaid expenses	4	4,540	3,862
Short term investments	5	147,996	119,414
Cash and cash equivalents		35,809	15,196
CURRENT LIABILITIES			
Creditors: amounts falling due within one year	6	(1,606)	(5,727)
NET CURRENT ASSETS		202,633	169,273
TOTAL ASSETS LESS CURRENT LIABILITIES		202,633	448,898
Creditors: amounts falling due after more than one year	7	(32,086)	(20,204)
NET ASSETS		170,547	428,694
CAPITAL AND RESERVES			
Called up share capital	8	16,243	12,497
Share premium account		486,382	339,435
Share compensation reserve		143,794	115,062
Other comprehensive income		(137)	83
Accumulated losses		(475,735)	(38,383)
TOTAL EQUITY		170,547	428,694

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 2021 was a loss of $437.4 million (2020: loss of $801.8 million).

The parent company financial statements on pages 108-118 were approved by the Board of Directors on 25 April 2022 and were signed on its behalf by:

Hubert Gaspar
Director
25 April 2022
Registered number: 11494381

Parent Company Statement of Changes in Equity

for the year ended 31 December 2021

	Shares Number	Called Up Share Capital $'000	Share Premium Account $'000	Share Compensation Reserve $'000	Other Comprehensive Income $'000	(Accumulated losses)/ Retained Earnings $'000	Total $'000
At 1 January 2020	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
Issue of shares under employee equity plans	2,024,241	263	2,650	–	–	–	2,913
Issuance of shares under collaboration agreements	1,227,738	170	3,965	–	–	–	4,135
Issuance of shares under consulting agreement	22,758	3	(3)	–	–	–	–
Issuance of shares from private placement	24,115,755	3,310	146,690	–	–	–	150,000
Issuance costs	–	–	(6,355)	–	–	–	(6,355)
Share-based compensation	–	–	–	28,732	–	–	28,732
Unrealized loss on marketable securities	–	–	–	–	(220)	–	(220)
Loss for the year	–	–	–	–	–	(437,352)	(437,352)
Balance at 31 December 2021	125,674,095	16,243	486,382	143,794	(137)	(475,735)	170,547

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 company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. The Group'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 Group'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 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 UK Statutory Directors' Report. In addition, the Parent Company acknowledges its responsibility to support its subsidiaries' cash outflows for the foreseeable future. At 31 December 2021 the Group held cash, cash equivalents, and marketable securities of $220.1 million, and the Company held cash, cash equivalents, and marketable securities of $183.8 million. The Directors have prepared a forecast through the end of 2023 and expect that cash, cash equivalents, and marketable securities on hand as of 31 December 2021, 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 on a straight-line basis, 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, and prepayments where consideration has been paid for a service at a point in time but the service is received over a period of time. Debtors are recognised initially at fair value and subsequently measured at amortised cost using the effective interest method, less provision for impairment.

SHORT TERM INVESTMENTS

Short term investments 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. 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, and receivable from, subsidiary

Management perform an annual impairment assessment of the investment held in, and receivable due from, 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, 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. In 2021 an impairment of $305.9 million and $121.2 million have been recognised against the investment in subsidiary and receivable from subsidiary respectively.

2. INVESTMENTS

	Subsidiary undertakings ($000)
As at 1 January 2021	**279,625**
Share-based payments associated with subsidiary employees	26,323
Provision for impairment	(305,948)
As at 31 December 2021	**–**

	Subsidiary undertakings ($000)
Cost and net book value	**1,098,793**
Accumulated provision for impairment	(1,098,793)
As at 31 December 2021	**–**

Share-based payment cost of $26.3 million in 2021 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.

As the market capitlisation of the Group declined further in 2021 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 2021, and the Parent Company concluded that the investment was impaired by $305.9 million (2020: $792.8 million). 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 to reflect any improvement in the underlying business of the Group.

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
Orchard Therapeutics (Switzerland) 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., Orchard Therapeutics (Germany) GmbH and Orchard Therapeutics (Switzerland) 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	Basisweg 10, 1043 AP, Amsterdam, Netherlands
Orchard Therapeutics (France) SAS	France	23 rue du Roule 75001, Paris, France
Orchard Therapeutics (Italy) S.r.l	Italy	Largo Guido, Donegani 2 Cap 20121, Milano (MI), Italy
Orchard Therapeutics (Germany) GmbH	Germany	TRIBES Dusseldorf GAP, Graf-Adolf-Platz 15, 40213 Dusseldorf, Germany
Orchard Therapeutics (Switzerland) GmbH	Switzerland	KD Zug-Treuhand AG Untermüli 7 6300 Zug

3. DEBTORS

	2021 $000	2020 $000
Amounts owed by subsidiary undertakings	14,957	35,415
Other receivables	937	1,113
	15,894	**36,528**

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

The Company has an unrecognised deferred tax asset of $5.9 million at 31 December 2021 (2020: $1.9 million).

4. PREPAID EXPENSES

	2021 $000	2020 $000
Deferred financing costs	693	975
Prepaid expenses	3,847	2,887
	4,540	**3,862**

5. SHORT TERM INVESTMENTS

	2021 $000	2020 $000
Commercial Paper	64,406	35,462
Corporate Bonds	83,590	83,952
	147,996	**119,414**

Investments in commercial paper have fixed coupon rates at 0.1–0.3% (2020: 0.08–0.32%) and mature between 1 January 2022 and 30 November 2022 (2020: 1 January 2021 and 31 October 2021).

Investments in corporate bonds have fixed coupon rates at 0.2–3.2% (2020: 0.1–4.5%) and mature between 1 January 2022 and 31 October 2023 (2020: 1 January 2021 and 31 July 2022).

6. CREDITORS: amounts falling due within one year

	2021 $000	2020 $000
Bank loans and overdrafts	786	4,861
Trade creditors	308	270
Accruals	512	596
	1,606	**5,727**

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

Prior to execution of the Amended Credit Facility, each term loan under the Original Credit Facility bore interest at an annual rate equal to 6.0% plus LIBOR. The Company was required to make interest-only payments on the term loan for all payment dates prior to 24 months following the date of the Original Credit Facility, unless the third tranche was drawn, in which case for all payment dates prior to 36 months following the date of the Original Credit Facility. The term loans prior to the Amended Credit Facility were to begin amortizing on either the 24-month or the 36-month anniversary of the Original Credit Facility (as applicable), with equal monthly payments of principal plus interest to be made by the Borrower to the Lenders in consecutive monthly instalments until the loan maturity

date. In addition, a final payment of 4.5% was due on the loan maturity date. The Company accrued the final payment amount of $1.1 million associated with the first term loan of the Original Credit Facility, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the date of the Amended Credit Facility. Upon execution of the Amended Credit Facility, the Company was required to make a payment of $0.5 million for the accrued final payment associated with the Original Credit Facility, which was netted against proceeds from the additional initial term loan.

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

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

As of 31 December 2021 and 2020, bank loans consist of the following:

	2021 $000	2020 $000
Notes payable, net of unamortized debt issuance costs	32,669	24,659
Less: current portion	(786)	(4,861)
Notes payable, net of current portion	**31,883**	**19,798**
Accretion related to final payment	203	406
Bank loans and overdrafts, long term	**32,086**	**20,204**

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

	Aggregate Minimum Payments $000
2022	786
2023	9,429
2024	9,429
2025	9,429
2026	5,082
Thereafter	–
Total payments	**34,155**
Less: current portion	(786)
Less: unamortized portion of final payment	(952)
Less: unamortized debt issuance costs	(331)
Bank loans and overdrafts, long term	**32,086**

Interest expense for the year ended 31 December 2021 was $2.5 million (2020: $2.3 million).

8. CALLED UP SHARE CAPITAL

	2021 $000	2020 $000
Ordinary shares alloted and fully paid, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 shares	16,243	12,497
	16,243	**12,497**

As of 31 December 2021 and 2020, the Company had authority to allot ordinary shares up to a maximum nominal value of £13,023,851.50 with a nominal value of £0.10 per share. As of 31 December 2021 and 2020, there were 125,674,095 and 98,283,603 ordinary shares issued and outstanding, respectively. As of 31 December 2021 and 2020, there were a total of 17,300,740 and 13,895,643 share options in respect of ordinary shares outstanding, respectively. In addition, as of 31 December 2021 and 2020, there were 318,333 and 644,000 unvested restricted share units outstanding in respect of ordinary shares outstanding, respectively.

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

In July 2021 the Company issued 1,227,738 ordinary shares to Pharming Group N.V. for total consideration of $7.5 million. The consideration is payment for the fair value of ordinary shares with a fair value of $4.1 million plus a $3.4 million premium on the fair value of the Company's ordinary shares, which was allocated to the license and collaboration agreement.

In December 2021, the Company issued 22,758 ordinary shares pursuant to a consulting agreement with a non-employee advisor.

During the year ended 31 December 2021, the Company issued 1,727,254 shares as a result of share option exercises, and 296,987 shares from our employee share purchase plan.

As of 31 December 2021 and 2020, 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 2021, the Company has not declared any dividends (2020: $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 20 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

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

ORCHARD THERAPEUTICS PLC
CONSOLIDATED FINANCIAL STATEMENTS
FOR THE YEAR ENDED 31 December 2021

Registered Number: 11494381

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

	December 31,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	$ 55,912	$ 55,135
Marketable securities	164,195	136,813
Accounts receivable	1,480	878
Prepaid expenses and other current assets	23,011	13,365
Research and development tax credit receivable	30,723	17,344
Total current assets	275,321	223,535
Non-current assets:		
Operating lease right-of-use-assets	24,316	29,815
Property and equipment, net	4,767	4,781
Restricted cash	4,266	4,266
Intangible assets, net	4,149	3,076
Other assets	9,590	15,464
Total non-current assets	47,088	57,402
Total assets	$ 322,409	$ 280,937
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 10,008	$ 8,823
Accrued expenses and other current liabilities	24,318	28,943
Deferred revenue	346	—
Operating lease liabilities	7,335	8,934
Notes payable, current	786	4,861
Total current liabilities	42,793	51,561
Notes payable, long-term	32,086	20,204
Deferred revenue, net of current portion	12,519	—
Operating lease liabilities, net of current portion	19,278	24,168
Other long-term liabilities	5,783	6,570
Total liabilities	112,459	102,503
Commitments and contingencies (Note 18)		
Shareholders' equity:		
Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 of shares at December 31, 2021 and 2020, respectively; 125,674,095 and 98,283,603 shares issued and outstanding at December 31, 2021 and 2020, respectively.	16,253	12,507
Additional paid-in capital	940,675	771,194
Accumulated other comprehensive income	3,246	373
Accumulated deficit	(750,224)	(605,640)
Total shareholders' equity	209,950	178,434
Total liabilities and shareholders' equity	$ 322,409	$ 280,937

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

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

	For the Year Ended December 31,	
	2021	2020
Product sales, net	$ 700	$ 2,595
Collaboration revenue	975	—
Total revenues	1,675	2,595
Costs and operating expenses		
Cost of product sales	226	857
Research and development	86,977	93,730
Selling, general and administrative	54,905	64,986
Total costs and operating expenses	142,108	159,573
Loss from operations	(140,433)	(156,978)
Other (expense) income:		
Interest income	412	3,185
Interest expense	(2,497)	(2,328)
Other (expense) income, net	(1,238)	3,411
Total other (expense) income, net	(3,323)	4,268
Net loss before income tax	(143,756)	(152,710)
Income tax (expense) benefit	(828)	731
Net loss attributable to ordinary shareholders	$ (144,584)	$ (151,979)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.17)	$ (1.53)
Weighted average number of ordinary shares outstanding, basic and diluted	123,963,762	99,445,874
Other comprehensive income (loss)		
Foreign currency translation adjustment	3,124	(1,485)
Unrealized loss on marketable debt securities	(251)	(184)
Total other comprehensive income (loss)	2,873	(1,669)
Total comprehensive loss	$ (141,711)	$ (153,648)

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

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

	Ordinary shares		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
	Shares	Amount				
Balance at December 31, 2019	**96,923,729**	**$ 12,331**	**$ 738,481**	**$ 2,042**	**$ (453,661)**	**$ 299,193**
Share-based compensation expense	—	—	27,962	—	—	27,962
Exercise of share options	1,154,441	149	3,316	—	—	3,465
Issuance of ESPP shares	107,262	14	657	—	—	671
Ordinary shares issued as part of consulting agreement	22,758	3	(3)	—	—	—
Ordinary shares issued as part of license agreement	75,413	10	781			791
Foreign currency translation	—	—	—	(1,485)	—	(1,485)
Unrealized gain on marketable debt securities	—	—	—	(184)	—	(184)
Net loss	—	—	—	—	(151,979)	(151,979)
Balance at December 31, 2020	**98,283,603**	**$ 12,507**	**$ 771,194**	**$ 373**	**$ (605,640)**	**$ 178,434**
Share-based compensation expense	—	—	22,536	—	—	22,536
Exercise of share options	1,727,254	224	2,515	—	—	2,739
Issuance of ESPP shares	232,340	30	534	—	—	564
Vesting of restricted share units, net of shares withheld for taxes	64,647	9	(401)	—	—	(392)
Sale of voting and non-voting ordinary shares, net of issuance costs of $6,355	24,115,755	3,310	140,335	—	—	143,645
Ordinary shares issued as part of consulting agreement	22,758	3	(3)	—	—	—
Ordinary shares issued as part of collaboration agreement	1,227,738	170	3,965	—	—	4,135
Foreign currency translation	—	—	—	3,124	—	3,124
Unrealized loss on marketable debt securities	—	—	—	(251)	—	(251)
Net loss	—	—	—	—	(144,584)	(144,584)
Balance at December 31, 2021	**125,674,095**	**$ 16,253**	**$ 940,675**	**$ 3,246**	**$ (750,224)**	**$ 209,950**

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

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

	Year Ended December 31,	
	2021	2020
Cash flows from operating activities		
Net loss attributable to ordinary shareholders	$ (144,584)	$ (151,979)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	2,327	2,004
Share-based compensation	22,536	27,962
Impairment of long-lived assets	—	5,650
Non-cash interest expense	392	500
Amortization of provision on loss contract	(1,037)	(2,413)
Non-cash consideration for licenses and milestones	—	791
Deferred income taxes	1,131	(2,257)
Amortization of premium on marketable securities	1,514	770
Unrealized foreign currency and other non-cash adjustments	9,687	(3,674)
Changes in operating assets and liabilities:		
Accounts receivable	(624)	582
Research and development tax credit receivable	(13,920)	11,674
Prepaid expenses, other current assets, and other assets	(5,209)	(5,070)
Operating leases, right-of-use-assets	5,938	5,863
Accounts payable, accrued expenses, and other current liabilities	(9,452)	(12,278)
Deferred revenue	13,122	—
Other long-term liabilities	34	2,570
Operating lease liabilities	(6,952)	(6,969)
Net cash used in operating activities	$ (125,097)	$ (126,274)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	234,732	281,433
Purchases of marketable securities	(263,878)	(113,262)
Payment of construction deposit	—	(10,000)
Receipt of funds from construction deposit	216	1,876
Payments on intangible assets	(887)	—
Purchases of property and equipment	(2,348)	(2,668)
Net cash (used in) provided by investing activities	$ (32,165)	$ 157,379
Cash flows from financing activities		
Proceeds from modification of credit facility, net of debt issuance costs paid	7,375	—
Proceeds from employee equity plans	3,303	3,936
Payment of taxes on restricted stock vesting	(392)	—
Proceeds from issuance of shares as part of collaboration agreement	4,135	—
Proceeds from the issuance of ordinary shares in private placement	150,000	—
Payment of placement agent fees and offering costs	(6,355)	—
Net cash provided by financing activities	$ 158,066	$ 3,936
Effect of exchange rate changes on cash	(27)	1,043
Net increase in cash, cash equivalents and restricted cash	$ 777	$ 36,084
Cash, cash equivalents, and restricted cash —beginning of year	59,401	23,317
Cash, cash equivalents, and restricted cash —end of year	$ 60,178	$ 59,401
Supplemental disclosure of non-cash investing and financing activities		
Intangible assets and property and equipment in accounts payable and accrued expenses	2,589	3,096
Shares issued in consideration of license agreements	—	791
Employee equity plan proceeds received after year-end	—	200
Supplemental disclosure of cash flow information		
Lease assets obtained in exchange for new operating lease liabilities	552	17,486
Cash paid for interest	2,103	1,828
Cash paid for taxes	1,651	1,007

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

1. Nature of Business and Basis of Presentation

Orchard Therapeutics plc (the "Company") is a global gene therapy company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. The Company's *ex vivo* autologous hematopoietic stem cell ("HSC") gene therapy approach utilizes genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Company's gene therapy product candidate pipeline spans multiple therapeutic areas where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

The Company is a public limited company incorporated pursuant to the laws of England and Wales. The Company has American Depositary Shares ("ADSs") registered with the U.S. Securities and Exchange Commission (the "SEC") and has been listed on the Nasdaq Global Select Market since October 31, 2018. The Company's ADSs each represent one ordinary share of the Company.

In December 2020, the Company received standard marketing authorization from the European Commission for Libmeldy™ (atidarsagene autotemcel), for the treatment of early onset metachromatic leukodystrophy ("MLD"), characterized by biallelic mutations in the *arylsulfatase-A* (*ARSA*) gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

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

The Company's business is subject to risks and uncertainties common to development-stage companies in the biotechnology industry. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's technology will be obtained, that any products developed will obtain necessary government regulatory approval or that any products, if approved, will be commercially viable. The Company operates in an environment of rapid technological innovation and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and service providers. Even if the Company's product development efforts are successful in gaining regulatory approval, it is uncertain when, if ever, the Company will realize significant revenue from product sales. The future developments of the COVID-19 pandemic may also directly or indirectly impact the Company's business, including impacts due to quarantines, border closures, increased border controls, travel restrictions, shelter-in-place orders and shutdowns, business closures, cancellations of public gatherings and other measures.

The accompanying consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Through December 31, 2021, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares, and ADSs in the IPO and follow-on offering. The Company has incurred recurring losses since its inception, including net losses of $144.6 million and $152.0 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, the Company had an accumulated deficit of $750.2 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expects that its cash, cash equivalents, and marketable securities on hand as of December 31, 2021 of $220.1 million will be sufficient to fund its operations and capital expenditure requirements for at least the next twelve months. The Company will seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into collaborations or other arrangements. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. The future viability of the Company is dependent on its ability to raise additional capital to finance its

operations. If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Basis of presentation

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

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

2. Summary of Significant Accounting Policies

Principles of consolidation

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

Use of estimates

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

Concentration of credit risk

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

Foreign currency

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. Dollar are translated into U.S. Dollars using period-end exchange rates for assets and liabilities, historical exchange rates for shareholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in shareholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations. The Company recorded realized and unrealized foreign currency transaction losses of $1.2 million, and gains of $3.4 million for the years ended December 31, 2021, and 2020, respectively, which is included in other income (expense) in the statements of operations and comprehensive loss.

Segment information

The Company operates in a single segment, focusing on researching, developing and commercializing potentially curative gene therapies. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of the Company's operations are reported on a consolidated basis for purposes of segment reporting. All material long-lived assets of the Company reside in the United States or United Kingdom. The Company had property and equipment of $3.6 million and $1.2 million located in the United Kingdom and United States, respectively, as of December 31, 2021. The Company had property and equipment of $3.7 million and $1.1 million located in the United Kingdom and United States, respectively, as of December 31, 2020. The Company had right-of-use assets in the United States and United Kingdom and European Union of $12.5 million and $11.8 million, respectively, as of December 31, 2021. The Company had right-of-use assets in the United States and United Kingdom and European Union of $14.2 million and $15.6 million, respectively, as of December 31, 2020.

Cash equivalents

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

Marketable securities

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

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

Restricted cash and construction deposits

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on our consolidated balance sheet. The Company has an outstanding letter of credit for $3.0 million associated with a lease, and is required to hold this amount in a standalone bank account at December 31, 2021 and 2020. The Company is also contractually required to maintain a cash collateral account associated with corporate credit cards and other leases in the amount of $1.3 million at December 31, 2021 and 2020.

The Company includes the restricted cash balance in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the consolidated statements of cash flows. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported in the consolidated balance sheet that sum to the total of the amounts reported in the consolidated statement of cash flows:

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

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

Inventory

Inventory is stated at the lower of cost or estimated net realizable value with cost determined on a first-in, first-out basis. Inventory costs include raw materials, third-party contract manufacturing, third-party packaging services, and freight. Raw and intermediate materials that may be utilized for either research and development or commercial purposes are classified as inventory. Amounts in inventory that are used for research and development purposes are charged to research and development expense when the product enters the research and development process and can no longer be used for commercial purposes and, therefore, does not have an "alternative future use" as defined in authoritative guidance. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period and, if needed, writes down any excess and obsolete inventory to its estimated net realizable value in the period it is identified. If they occur, such impairment charges are recorded as a component of cost of goods sold in the consolidated statements of operations and comprehensive income (loss). Inventory is included in prepaid expenses and other current assets on the consolidated balance sheets and the amount was not significant as of December 31, 2021.

Prior to the initial date that regulatory approval is received, costs related to the production of inventory are recorded as research and development expense on the Company's consolidated statements of operations and comprehensive income (loss) in the period incurred. In connection with the acquisition of Strimvelis in April 2018, and with the EMA approval of Libmeldy in December 2020, the Company subsequently began capitalizing inventory manufactured or purchased after these dates.

Intangible assets, net

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

Property and equipment

Property and equipment are recorded at cost and depreciated or amortized using the straight-line method over the following estimated useful lives.

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

Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property and equipment, are expensed as incurred. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts, and any resulting gain or loss is included in the consolidated statements of operations and other comprehensive loss.

Impairment of long-lived assets

Long-lived assets consist of property and equipment and operating lease right-of-use assets. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or

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

Research and development costs

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

Research contract costs and accruals

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

Share-based compensation

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

Comprehensive loss

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

Leases

The Company determines if an arrangement is a lease at contract inception. Operating lease assets represent a right to use an underlying asset for the lease term and operating lease liabilities represent an obligation to make lease payments arising from the lease. Operating lease liabilities with a term greater than one year and their corresponding right-of-use assets are recognized on the balance sheet at the commencement date of the lease based on the present value of lease payments over the expected lease term. Certain adjustments to the right-of-use asset may be required for items such as initial direct costs paid or incentives received. The Company made an accounting policy election to not record a right-of-use asset or lease liability for leases with a term of one year or less. To date, the Company has not identified any material short-term leases, either individually or in the aggregate.

As the Company's leases do not provide an implicit rate, the Company utilized the appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term as the lease an amount equal to the lease payments in a similar economic environment. The Company estimated the incremental borrowing rate based on the

Company's currently outstanding credit facility as inputs to the analysis to calculate a spread, adjusted for factors that reflect the profile of secured borrowing over the expected term of the lease.

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

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

Strimvelis loss provision

As part of the GSK transaction, the Company is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available (see Note 15). Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company initially recorded a liability associated with the loss contract of $18.4 million in 2018. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with the Strimvelis program and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a credit to research and development expense. The Company has made an estimate of the expected future losses associated with Strimvelis and will adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of the future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for the updated future losses.

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

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

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

United Kingdom Research and development income tax credits

As a company that carries out research and development activities, the Company is able to submit tax credit claims from two UK research and development tax relief programs, the SME program and the RDEC program depending on eligibility. Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income.

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

programs, that it plans to submit a claim for, and it has reasonable assurance that the amount will ultimately be realized. Based on criteria established by HM Revenue and Customs ("HMRC"), management of the Company expects a proportion of expenditures being undertaken in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for the research and development tax relief programs for the year ended December 31, 2021. The Company has qualified under the more favorable SME regime for the year ended December 31, 2020 and expects to qualify under the SME regime for the year ending December 31, 2021.

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

The Company recognizes credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expense. The following table outlines the changes to the research and development tax credit receivable, including amount recognized as an offset to research and development expense during the years ended December 31, 2021 and 2020:

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

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

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

Income taxes

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

The Company accounts for income taxes in accordance with ASC Topic 740, *Accounting for Income Taxes*, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. The Company determines its deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the net deferred tax assets will not be realized.

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

Product sales

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

Collaboration revenue

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

The Company first evaluates collaboration arrangements to determine whether the arrangement (or part of the arrangement) represents a collaborative arrangement pursuant to ASC Topic 808, *Collaborative Arrangements*, based on the risks and rewards and activities of the parties pursuant to the contractual arrangement. The Company accounts for any collaborative arrangement or elements within the contract that are deemed to be a collaborative arrangement, and not a customer relationship, in accordance with ASC 808. Through December 31, 2021, the Company entered into one agreement with Pharming Group N.V. (the "Pharming Agreement", see Note 16) that is accounted for pursuant to ASC 606.

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

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

The Pharming Agreement entitles the Company to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, regulatory milestones, and sales-based milestones. The Company is also eligible to receive from Pharming tiered royalty payments on worldwide net sales. The Company evaluates whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within the Company's control, are considered constrained until such approval is received. Upfront and ongoing development milestones per the collaboration agreements are not subject to refund if the development activities are not successful. At the end of each subsequent reporting period, the Company re-evaluates the probability of a significant reversal of the cumulative revenue recognized for the milestones, and, if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators in

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

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

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

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

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

Net loss per share

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

The following securities, presented based on amounts outstanding at each period end, are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti-dilutive:

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

Recent accounting pronouncements

In November 2021, the FASB issued ASU No. 2020-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance*, which requires increased transparency in the disclosures about government assistant in the notes to the financial statements. This ASU is effective for the Company beginning January 1, 2022, and interim periods within that year, with early adoption permitted. The Company does not expect this amendment to have a significant effect on its financial statement disclosures.

3. Fair Value Measurements and Marketable Securities

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

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

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

The 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
U.S. government securities	—	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 carrying amount reflected in the consolidated balance sheets for research and development tax incentive receivable, trade receivables, other receivables, accounts payable, and accrued expenses approximate fair value due to their short-term maturities. The carrying value of the Company's outstanding notes payable approximates fair value (a Level 2 fair value measurement), reflecting interest rates currently available to the Company.

Marketable Securities

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

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

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

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

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

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

4. Product sales

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

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

5. Prepaid expenses and other current assets

Prepaid expenses and other current assets consist of the following:

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

6. Property and equipment

Property and equipment consist of the following:

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

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

7. Intangible assets, net

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

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

License intangibles consist of capitalized milestone payments or accruals of payments the Company has deemed probable upon receiving regulatory approval of Libmeldy in the EU. The license intangibles are being amortized on a straight-line basis over the remaining useful life of the related patents of approximately twelve years. For year ended December 31, 2021, amortization of intangible assets totaled $0.2 million. For the year ended December 31, 2020, amortization of intangible assets was nil. The effect of foreign currency translation on the net carrying value of intangible assets during 2021 was not material.

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

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

8. Other assets

Other assets consist of the following:

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

9. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

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

10. Restructuring charges

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

Cash restructuring charges

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

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

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

Impairment of long-lived assets

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

	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 11). No further impairment was necessary as a result of the sublease. The occurrence of a triggering event for the Fremont ROU asset in future periods could result in additional impairment charges if the estimated fair value of the asset is determined to be lower than the carrying value.

11. Leases

Operating leases

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

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

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

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

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

As of December 31, 2021, the carrying value of the operating lease right-of-use assets in Boston and London was $4.1 million and the lease liabilities was $4.3 million. As of December 31, 2020, the carrying value of the operating lease right-of-use assets in Boston and London was $5.4 million and the lease liabilities was $5.7 million.

Fremont operating lease and sublease agreements

In December 2018, the Company leased manufacturing, laboratory, and office space in Fremont, California (the "Fremont facility" and the "Head Lease") which terminates in May 2030. In May 2020, the Company committed to a restructuring plan (see Note 10) whereby we ceased construction and build-out of the Fremont facility. In December 2020, the Company entered into a sublease agreement (the "Sublease") with an unrelated third-party (the "subtenant") whereby the Company subleased the entire Fremont facility to the subtenant. The Company accounts for the Head Lease and Sublease as two separate contracts. Both the Head Lease and Sublease were determined to be operating leases.

The Head Lease annual rental payments, including variable payments, were $3.1 million in 2021 and 2020. The Head Lease includes annual rent escalation provisions. The Company was provided with 8 months of free rent. Subject to the terms of the Head Lease agreement, the Company executed a $3.0 million letter of credit upon signing the lease, which may be reduced by 25% subject to reduction requirements specified therein. This amount is classified as restricted cash on the consolidated balance sheets.

As of December 31, 2021, the carrying value of the Fremont Head Lease right-of-use asset was $9.5 million and the lease liability was $13.1 million. The Head Lease provides for up to $5.3 million in tenant improvement allowances to be reimbursed to the Company by the landlord. These tenant improvement allowances have been included in the calculation of the operating lease liability and is currently expected to be received in 2022. The Company continues to assess the expected receipt of the tenant improvement allowances and may remeasure the right-of-use asset and liability from time to time as facts and circumstances may change.

The Sublease commenced in December 2020 and is in force for the remainder of the Head Lease term, through May 2030. The Sublease provides for 12 months of free rent until December 2021. The sublease provides for an initial annual cash base rent of $2.2 million, with annual rent escalation provisions. The subtenant is also responsible for paying all operating expenses associated with the Head Lease. The Sublease also includes pass-through of up to $5.3 million in tenant improvement allowances to the subtenant, subject to the Company being reimbursed for the allowances per the terms of the Head Lease. The Subtenant provided the Company with a $2.6 million security deposit, which may be converted to a letter of credit upon providing evidence of $2.6 million in construction expenditures. The Company accounts for the security deposit within other long-term liabilities.

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

Embedded operating lease arrangement

The Company is party to a manufacturing agreement for research and development and commercial production with AGC Biologics, S.p.A. (formerly MolMed S.p.A.) ("AGC") pursuant to which AGC will develop, manufacture and supply certain viral vectors and conduct cell processing activities for certain Company development and commercial programs. A manufacturing agreement with AGC was novated to the Company as part of the GSK Agreement (see Note 15). On July 2, 2020 (the "Effective Date"), the Company entered into a new manufacturing and technology development master agreement with AGC (the "AGC Agreement") which superseded the novated agreement.

The Company determined that the AGC Agreement contains an embedded lease as it includes provision of manufacturing suites designated for the Company's exclusive use during the term of the agreement. The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The agreement may be extended for an additional two years by mutual agreement of the Company and AGC. The AGC Agreement contains payments associated with lease and non-lease components. The contractual annual rental payments associated with the lease that are considered a lease component amount to €2.7 million per contract year. The non-lease components of the agreement consist of minimum manufacturing purchase requirements and dedicated manufacturing and development services (see Note 18).

As of December 31, 2021, the carrying value of the embedded operating lease right-of-use asset was $10.7 million and the lease liability was $9.3 million. As of December 31, 2020, the carrying value of the embedded operating lease right-of-use asset was $13.9 million and the lease liability was $13.1 million. The Company may terminate the AGC Agreement and the use of the exclusive manufacturing suites, with 12-months' notice, and beginning no earlier than July 2, 2022. AGC may terminate the AGC Agreement with 24-months' notice. The AGC Agreement provides for an option to reserve one additional exclusive manufacturing suite any time prior to January 1, 2022 for a one-time option fee plus annual rental fee. The AGC Agreement extends until July 2, 2025.

Summary of all lease costs recognized under ASC 842

Our facility leases described above generally contain customary provisions allowing the landlords to terminate the leases if we fail to remedy a breach of any of our obligations under any such lease within specified time periods, or upon our bankruptcy or insolvency. The leases do not include any restrictions or covenants that had to be accounted for under the lease guidance. The following table contains a summary of the lease-related costs recognized within operating expenses, and other information pertaining to the Company's operating leases as of December 31, 2021 and 2020:

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

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

During the year ended December 31, 2021, the Company obtained right of use assets valued at $0.6 million in exchange for lease liabilities of $0.6 million. During the year ended December 31, 2020 the Company obtained $17.5 million in right of use assets in exchange for $17.5 million in lease liabilities.

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

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

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

12. Notes Payable

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

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

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

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

debt by charges to interest expense using the effective-interest method from the date of issuance through the loan maturity date.

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

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

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

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

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

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

13. Shareholders' Equity and Convertible Preferred Shares

Ordinary shares

As of December 31, 2021, and 2020, each holder of ordinary shares and ADSs is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. As of December 31, 2021, and 2020, the Company has not declared any dividends.

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

Ordinary share issuances

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

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

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

In July 2021 the Company issued 1,227,738 ordinary shares to Pharming Group N.V. for total consideration of $7.5 million. The consideration is payment for the fair value of ordinary shares with a fair value of $4.1 million plus a $3.4 million premium on the fair value of the Company's ordinary shares, which was allocated to the license and collaboration agreement (see Note 16).

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

14. Share-based Compensation

The Company maintains four equity compensation plans; the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"), the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "2018 Plan"), the 2018 Employee Share Purchase Plan (the "ESPP"), and the 2020 Inducement Equity Plan (the "Inducement Plan"). The number of shares of common stock that may be issued under the 2018 Plan is subject to increase by the number of shares forfeited under any options forfeited and not exercised under the 2018 Plan or 2016 Plan. The board of directors has determined not to make any further awards under the 2016 plan. As of December 31, 2021, 6,934,474 shares remained available for grant under the 2018 Plan, 721,500 remained available under the Inducement Plan, and 1,197,399 shares remained available for grant under the ESPP.

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

Share options

The fair value of each stock option award is determined on the date of grant using the Black-Scholes option-pricing model. The risk-free interest rate is based on a U.S. treasury instrument whose term is consistent with the expected term of the stock options. The expected term of the Company's options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including those in the early stages of product development with a similar and therapeutic focus. For these analyses, the Company selects companies with comparable characteristics to its own

including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected term of the options. The relevant data used to determine the value of stock option awards are as follows:

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

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

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

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's ordinary shares for those options that had exercise prices lower than the fair value of the Company's ordinary shares. During the years ended December 31, 2021 and 2020, the total intrinsic value of share options exercised was $7.4 million and $5.0 million, respectively. During the years ended December 31, 2021 and 2020, the total proceeds to the Company from share options exercised was $2.7 million and $3.9 million, respectively. As of December 31, 2021, and 2020, there was $nil and $0.2 million in employee equity plan proceeds received after year-end, respectively.

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

Restricted Share Units

Performance-based share units

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

The fair value associated with the performance-based conditions is recognized when achievement of the milestones becomes probable, if at all. In the fourth quarter of 2020, the Company determined that a performance milestone was probable upon approval of Libmeldy by the European Commission in December 2020, and recognized $1.2 million in compensation cost. The shares associated with recognition of this performance milestone vested and were issued in January 2021.

CEO Award

The Company granted 195,000 performance-based RSUs with a total grant date fair value of $1.4 million to its Chief Executive Officer, Bobby Gaspar, M.D., Ph.D., in April 2020. The award vests on January 2, 2024 as to 1/3 of the award for each of the first three to occur of four milestones, if each such milestone is achieved by the Company on or before December

31, 2023 and Dr. Gaspar remains continuously employed with the Company through January 2, 2024. The milestones relate to achievement of specific clinical and regulatory milestones. No performance-based share unit performance conditions associated with the CEO award were deemed probable and none vested during the year ended December 31, 2021.

Time-based restricted share units

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

The following table summarizes restricted share unit award activity for the year-end December 31, 2021:

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

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,	
	2021	2020
Research and development	$ 9,214	$ 11,679
Selling, general and administrative	13,322	16,283
Total	$ 22,536	$ 27,962

The Company had 9,420,072 unvested options outstanding as of December 31, 2021. As of December 31, 2021, total unrecognized compensation cost related to unvested stock option grants and time-based RSUs was approximately $37.1 million. This amount is expected to be recognized over a weighted average period of approximately 2.77 years. As of December 31, 2021, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $1.4 million, the timing of recognition will be dependent upon achievement of milestones.

15. License and Research Arrangements

GSK asset purchase and license agreement

In April 2018, the Company completed an asset purchase and license agreement (the "GSK Agreement") with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon Foundation and San Raffaele Hospital ("Telethon-OSR"). The portfolio of programs and options acquired consisted of:

- Two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS;
- One earlier stage clinical gene therapy program for TDT;
- Strimvelis, the first autologous *ex vivo* gene therapy for ADA-SCID which was approved for marketing by the European Medicines Agency in 2016; and
- Option rights exercisable upon completion of clinical proof of concept studies for three additional earlier-stage development programs, which option rights have all subsequently lapsed.

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations. Total consideration was £94.2 million

($133.6 million at the acquisition date), which included an upfront payment of £10.0 million ($14.2 million at the acquisition date) and 12,455,252 convertible preferred shares of the Company issued to GSK at an aggregate value of £65.8 million ($93.4 million at the acquisition date), a loss contract on the Strimvelis program valued at £12.9 million ($18.4 million), an inventory purchase liability valued at £4.9 million ($6.9 million) and transaction costs of £0.6 million ($0.8 million). The Company allocated £94.2 million ($133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development). The convertible preferred shares were converted to ordinary shares as part of our IPO in November 2018.

The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher ("PRV") from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDT, the first of which GSK retained beneficial ownership over. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. For accounting purposes, as of December 31, 2021, the Company does not consider the attainment of a PRV from the United States Food and Drug Administration to be probable.

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

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis. The Company will also pay tiered royalty rates at a percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at a percentage from the high single-digits to low double-digit for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

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

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

Telethon-OSR research and development collaboration and license agreements

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

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses

of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement. The Company may pay up to an aggregate of approximately €31.0 million ($35.0 million at December 31, 2021) in milestone payments upon achievement of certain product development milestones for the program.

In May 2019, the Company entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Company an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's *ex vivo* autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I ("MPS-I"), including the Hurler variant. To date, Telethon-OSR received €17.0 million in upfront and milestone payments from the Company upon entering into the agreement and shortly thereafter, resulting in $19.4 million in in-process research and development expense. The Company is also required to make milestone payments contingent upon certain development, regulatory and commercial milestones are achieved and may pay up to €28.0 million ($31.7 million at December 31, 2021). Additionally, the Company will be required to pay Telethon a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

UCLB/UCLA License Agreement

In February 2016, and amended in July 2017, the Company completed the UCLB/UCLA license agreement, under which the Company has been granted exclusive and non-exclusive, sublicensable licenses under certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories.

In exchange for these rights, in 2016, the Company made upfront cash payments consisting of $0.8 million for the license to the joint UCLB/UCLA technology and $1.1 million for the license to the UCLB technology and manufacturing technology. The Company also issued an aggregate of 4,665,384 ordinary shares to UCLB, of which 1,224,094, and 3,441,290 ordinary shares were issued in 2017 and 2016, respectively. The Company recorded research and development expense based on the fair value of the ordinary shares as of the time the agreement was executed or modified. The Company was also obligated to make an additional cash payment for clinical data. In 2017, the Company paid $0.8 million in relation to clinical data acquired. The Company recorded the payments to research and development expense.

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

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

In June 2021, the Company terminated the license to its OTL-101 program for ADA-SCID, which was granted pursuant to the UCLB/UCLA license agreement. Except for the termination of such license, the UCLB/UCLA license agreement continues in full force and effect.

Unless terminated earlier by either party, the UCLB/UCLA license agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, and as amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors to the Company ("Oxford BioMedica Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and fourth milestones were achieved, and the Company issued 150,826 ordinary shares. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million, which was expensed to research and development expense. No milestones were met during the year ended December 31, 2021.

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

16. Collaboration agreement with Pharming Group N.V.

Overview

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

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

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

Share Purchase Agreement

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

The "Collaboration Agreement" and the "SPA" are referred to together as the "Pharming Agreements."

Accounting Analysis

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 1,227,738 of the Company's ordinary shares as part of the SPA, and the license and collaboration agreement, which conveys the license and provides for the Company to provide research, development, manufacturing services for OTL-105. The Pharming Agreements were entered into concurrently as part of a single commercial objective, and the Company considers them a single arrangement for accounting purposes. The total upfront payments of $17.5 million are comprised of $4.1 million attributed to the equity sold to Pharming and $13.4 million attributed to the Collaboration Agreement. In determining the fair value of the common stock issued to Pharming as part of the SPA, the Company used an option pricing valuation model to take into consideration certain holding period restrictions on the shares. The fair value of the Company's common shares was considered a level 2 fair value measurement within the fair value hierarchy. The most significant assumptions within the model are the Company's stock price, the term of the restrictions and the stock price volatility, which is based upon historical volatility of the Company's stock. Based on the fair value adjustments made by management, the fair value of the shares issued was determined to be $4.1 million with the excess proceeds of $3.4 million being allocation to the Collaboration Agreement.

The Company recognizes revenue under Accounting Standards Codification ("ASC") 606, *Revenue from Contracts with Customer* ("ASC 606"). The Company has concluded that the conveyance of the license for the HAE program and the provision of research, development, and manufacturing services for the HAE program represent a series of distinct services that are accounted for as a single performance obligation within the Collaboration Agreement. The Company determined that the transaction price includes: the non-refundable up-front payment of $10.0 million, the $3.4 million in premium associated with the SPA, and the variable consideration for estimated reimbursement payments at agreed upon contractual rates to be received from Pharming for the Company's on-going research, development, and manufacturing services. The potential future variable consideration is associated with the reimbursement for research, development, and manufacturing services provided by the Company to Pharming at agreed upon contractual rates which is the only remaining unsatisfied performance obligation. The milestone payments included in the Collaboration Agreement are fully constrained, as a result of the uncertainty regarding whether any of the associated milestones will be achieved and therefore, the Company determined that it could not assert that it was probable that a significant reversal in the amount of cumulative revenue recognized will not

occur. The total estimated cost of the research and development services reflect the nature of the services to be performed and the Company's best estimate of the length of time required to perform the services. The Company re-evaluates the transaction price as of the end of each reporting period.

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

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

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

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

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

As of December 31, 2021, the Company had contract liabilities of $12.9 million, which is classified as either current or long-term deferred revenue in the consolidated balance sheets based on the period over which this is expected to be recognized. The deferred revenue balance represents the portion of the upfront payments received related to the performance obligation that remains partially unsatisfied as of December 31, 2021.

17. Income Taxes

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

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

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

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

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

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

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

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

The Company accounts for income taxes in accordance with ASC Topic 740. Deferred income tax assets and liabilities are determined based upon temporary differences between the financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The following table presents the principal components of the Company's deferred tax assets and liabilities as of December 31, 2021 and 2020:

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

For the years ended December 31, 2021 and 2020, the Company had cumulative tax-effected UK net operating loss carryforwards of approximately $126.6 million and $75.1 million, respectively. UK losses not surrendered may be carried forward indefinitely, subject to numerous utilization criteria and restrictions and are fully offset by a valuation allowance. For the years ended December 31, 2021 and 2020, the Company also had U.S. federal orphan drug tax credits of $0.6 million and $0, respectively, and U.S. state research and development tax credits of $2.4 million and $2.0 million. The U.S. federal orphan drug tax credits expire in 2041, while the U.S. state research and development credits may be carried forward indefinitely and are offset by a valuation allowance.

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

As of each reporting date, the Company considers new evidence, both positive and negative, that could impact the Company's view with regard to future realization of our deferred tax assets. Management has considered the Company's history of cumulative net losses in the UK, along with estimated future taxable income and has concluded that it is more likely than not that the Company will not realize the benefits of its UK deferred tax assets and U.S. state research and development tax credits. Accordingly, the Company has maintained a full valuation allowance against these net deferred tax assets as of December 31, 2021 and 2020, respectively.

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

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

The Company applies the authoritative guidance on accounting for and disclosure of uncertainty in tax positions, which requires the Company to determine whether a tax position of the Company is more likely than not to be sustained upon examination, including resolution of any related appeals of litigation processes, based on the technical merits of the position. For tax positions meeting the more likely than not threshold, the tax amount recognized in the financial statements is reduced by the largest benefit that has a greater than fifty percent likelihood of being realized upon the ultimate settlement with the relevant taxing authority. There were no material uncertain tax positions as of December 31, 2021 and 2020.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2021, and 2020, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statement of operations.

The Company and its subsidiaries file income tax returns in the UK, the U.S., and various foreign jurisdictions. Generally, the tax years 2017 through 2021 remain open to examination by the major taxing jurisdictions to which the Company is subject. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the federal, state, or foreign tax authorities, if such tax attributes are utilized in a future period.

18. Commitments and Contingencies

Lease commitments

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

Manufacturing and technology development master agreement with AGC

On July 2, 2020, the Company entered into the AGC Agreement, pursuant to which AGC will develop, manufacture and supply certain viral vectors and conduct cell processing activities for certain Company development and commercial programs. Under the terms of the AGC Agreement, the Company is obligated to pay AGC for a minimum product manufacturing commitment, dedicated manufacturing and development resources, and for a lease component associated with the right of use of exclusive manufacturing suites within AGC's existing facilities. The following table outlines the annual commitments associated with the contract, as of December 31, 2021:

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

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

(1) The minimum product manufacturing commitments may be increased to the mid-seven figures per contract year upon achievement of certain milestones.
(2) The Company may increase or decrease the usage of dedicated development services on a rolling basis with between six and 12-months' prior written notice to AGC. The above table assumes continued usage of dedicated development services at current rates.
(3) Refer to Note 11 for further information on the embedded operating lease agreement

The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The AGC Agreement may be extended for an additional two years by mutual agreement of the Company and AGC. The Company has the right to terminate the AGC Agreement at its discretion upon 12-month's prior written notice to AGC, and beginning no earlier than July 2, 2022, AGC has the right to terminate the AGC Agreement at its discretion upon 24-month's prior written

notice to the Company. Each party may terminate the AGC Agreement upon prior notice to the other party for an uncured material breach that the breaching party does not cure within the notice period.

Other funding commitments

The Company has entered into several license agreements (see Note 15). In connection with these agreements the Company is required to make milestone payments and annual license maintenance payments or royalties on future sales of specified products.

Consulting Agreement

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

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

Legal proceedings

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

19. Benefit Plans

The Company makes contributions to private defined contribution pension plans on behalf of its employees. The Company matches its employee contributions up to six percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid $1.7 million and $1.6 million, in matching contributions for the years ended December 31, 2021 and 2020, respectively.

20. Related-party Transactions

GSK

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

As of December 31, 2020, the Company had accounts payable and accrued expenses due to GSK of $0.1 million. During the year-ended December 31, 2020, the Company entered into a global license agreement with GSK for use of their lentiviral stable cell line technology whereby the Company recorded $1.2 million of in-process research and development expense associated with upfront payments made to GSK. During the year-ended December 31, 2020, the Company made $5.8 million in payments on accounts payable due to GSK associated with milestones, clinical inventory, and royalties.

21. Subsequent events

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