Orchard Therapeutics plc

Annual Report and Financial Statements
for the Year Ended 31 December 2022

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 Hubert Gaspar Charles Rowland Alicia Secor
Secretary	Christopher York
Registered Office	245 Hammersmith Road 3rd Floor London United Kingdom
Company Number	11494381
Independent Auditors	PricewaterhouseCoopers LLP 40 Clarendon Road Watford WD17 1JJ United Kingdom

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 2022 and of its loss and cash flows for the year then ended;
- have been properly prepared in accordance with UK-adopted international accounting standards; 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 Statement of Financial Position as at 31 December 2022; the Consolidated Statement of Profit or Loss, the Consolidated Statement of Comprehensive Loss, the Consolidated Statement of Changes in Equity, the Consolidated Cash Flow Statement 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 nine 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.

Key audit matters

- Expenses, accruals and prepayments for clinical research arrangements

Materiality

- Overall materiality: $8,096,000 (2021: $7,250,000) based on 5% of loss before taxation.
- Performance materiality: $6,072,000 (2021: $8,000,000).

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.

Expenses, accruals and prepayments for clinical research arrangements is a new key audit matter this year. Orchard Therapeutics (Europe) Limited Research & Development Tax Credit Receivable, which was a key audit matter last year, is no longer included because of the value of the balance has reduced significantly in the year such that the tax credit receivable and profit and loss account credit is no longer material to the financial statements.

Key audit matter	***How our audit addressed the key audit matter***
Expenses, accruals and prepayments for clinical research arrangements As described in notes 1 and 2 to the consolidated financial statements, the Group has entered into various research and development contracts with clinical research organisations (CROs) and clinical manufacturing organisations (CMOs). When billing terms under these contracts do not coincide with the timing of when the work is performed, management is first required to make estimates of the expense to be recognised in respect of the contracts such that the expense reflects the pattern of work performed. Subsequently, management is required to calculate the associated accrual or prepayment balance for each contract, based on the difference between the cumulative amount expensed under the contract to date and the cumulative amount invoiced to date. Given the difficult in estimating the stage of completion of a clinical trial, or with obtaining the required information from the CRO/CMO, this is considered an area of estimation uncertainty. The prepayment recorded for these arrangements as at 31 December 2022 is not material at just $881k, however the accrual amounts to $11.2m, with the relevant expense classified within "Research and development expenses" in the Consolidated Statement of Profit or Loss..	We have performed the following procedures to gain comfort over management's estimate for the expenses, accruals and prepayments for clinical research arrangements: – Reviewed contracts with CROs and CMOs to understand the arrangements and key terms. – Recalculated the expense to be recognised for a sample of contracts in the year based on contractual terms, third party evidence and in some cases, third party confirmation with the CRO. – Tested a sample of invoices received in the year from CROs/CMOs for accuracy, and that they have been correctly applied to the appropriate CRO/CMO in management's accounting model. – Recalculated the prepayment/accrual based on the difference between cumulative expense and cumulative invoicing, and reconciled this to management's workings. – Tested the completeness of costs recognised through contract reviews, review of publicly available information such as press releases and discussions with clinical personnel regarding the progress towards meeting contractual milestones which could trigger additional expense to be recognised. No exceptions were noted from our procedures performed over the expenses, accruals and prepayments for clinical research arrangements.

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.

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 nine 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 we performed 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, as well as a site visit to the UK from the PwC US team in December 2022.

The impact of climate risk on our audit

As part of our audit we made enquiries of management to understand the extent of the potential impact of climate risk on the group's financial statements, and we remained alert when performing our audit procedures for any indicators of the impact of climate risk. Our procedures did not identify any material impact as a result of climate risk on the group's financial statements.

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	$8,096,000 (2021: 7,250,000).
How we determined it	5% of loss before taxation
Rationale for benchmark applied	The group is loss making, as expected given its status as an early stage life sciences company with only two 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 $5,050,000 to $6,400,000. 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% (2021: 75%) of overall materiality, amounting to $6,072,000 (2021: $8,000,000) 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.

We agreed with those charged with governance that we would report to them misstatements identified during our audit above $405,000 (2021: $360,000) 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.

continued

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 2022 is consistent with the financial statements and has been prepared in accordance with applicable legal requirements.

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

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

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

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

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 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 UK tax legislation and 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.

continued

- Performing audit procedures over expenses, accruals and prepayment balances associated with third party contract research organisations (CROs), who perform clinical trials on behalf of the company.
- 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.

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 2022 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

27 April 2023

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 2022 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, including FRS 101 "Reduced Disclosure Framework", 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 2022; 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 the parent company, Orchard Therapeutics plc.

Key audit matters

- Valuation of investment in Orchard Therapeutics (Europe) Limited and expected credit loss provision against intercompany receivables

Materiality

- Overall materiality: $800,000 (2021: $2,042,000) based on 1% of total assets.
- Performance materiality: $600,000 (2021: $1,532,000).

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.

continued

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

The key audit matter below is consistent with last year.

Key audit matter	***How our audit addressed the key audit matter***
Valuation of investment in Orchard Therapeutics (Europe) Limited and expected credit loss provision against intercompany receivables As described in notes 1, 2 and 13 to the consolidated financial statements, the parent company holds an investment in its subsidiary, Orchard Therapeutics (Europe) Limited, and also has an intercompany receivable due from this subsidiary, which is termed "Amounts owed by subsidiary undertakings", classified within "Debtors" on the Parent Company Balance Sheet. The reduction in the market capitalisation of Orchard Therapeutics plc, based on the Group's share price at 31 December 2022, 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 2022 is below the carrying value of the investment and intercompany receivable due from Orchard Therapeutics (Europe) Limited. Having regard for the reduction in the market capitalisation of the Group, management has assessed that the investment in Orchard Therapeutics (Europe) Limited is not recoverable, and have therefore impaired the balance to nil as at 31 December 2022, with an impairment loss of $11m recognised in the year. In assessing the recoverability of the intercompany receivable due from Orchard Therapeutics (Europe) Limited, management has considered the probability of default and loss given default, if the amount was to be recalled at the Statement of financial position date. Given the fall in the market capitalisation of the Group and the impairment of the investment management has assessed there to be a high probability of default. A provision for expected credit losses of $114m has been recorded against the intercompany receivable such that the balance that remains represents what is deemed to be recoverable.	We have performed the following procedures over the impairment assessment which management has prepared: – Assessed management's impairment model and calculation for compliance with UK GAAP (FRS 101), including an assessment of the reasonableness of the probability of default and loss assessed 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 of the investment and expected credit loss in respect of the intercompany receivable to be recognised in the year. – 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.

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, certain procedures have been performed by PwC US as component auditors. We have instructed PwC US to report to us 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 101.

The impact of climate risk on our audit
As part of our audit we made enquiries of management to understand the extent of the potential impact of climate risk on the parent company's financial statements, and we remained alert when performing our audit procedures for any indicators of the impact of climate risk. Our procedures did not identify any material impact as a result of climate risk on the parent company's financial statements.

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	$800,000 (2021: $2,042,000).
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% (2021: 75%) of overall materiality, amounting to $600,000 (2021: $1,532,000) 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 $40,000 (2021: $102,000) 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 2022 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 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.

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

continued

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 2022.

Katherine Birch-Evans

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

27 April 2023

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 UK-adopted international accounting standards and the parent company financial statements in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 101 "Reduced Disclosure Framework", 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 UK-adopted international accounting standards have been followed for the group financial statements and United Kingdom Accounting Standards, comprising FRS 101 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 2022.

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

We are currently focusing our *ex vivo* autologous HSC gene therapy approach on severe neurometabolic diseases and early research programs. Our lead program is OTL-200, which was approved in the European Union, the United Kingdom, Iceland, Liechtenstein and Norway under the brand name Libmeldy for eligible patients with early-onset metachromatic leukodystrophy, or MLD. In advance of a potential Biologics License Application ('BLA') submission, Orchard Therapeutics is conducting a meeting with the U.S. Food and Drug Administration involving several specialized functions within the company and agency. The primary purpose of a pre-BLA meeting is to discuss the planned content of the marketing application. Pending the outcome of the multidisciplinary pre-BLA meeting scheduled for the second quarter of 2023, we anticipate a potential BLA submission in mid-2023.

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

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

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

in our registrational clinical trials. The registrational trials for all our earlier stage product candidates are expected to be conducted using a cryopreserved formulation.

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

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

Our *ex vivo* autologous HSC gene therapy approach

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

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

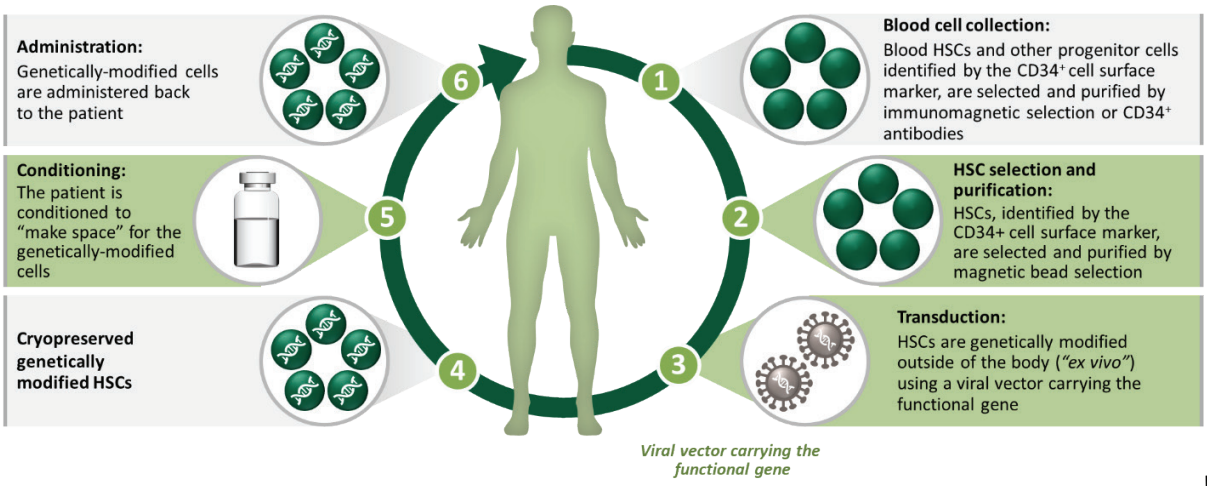
neuronal cells before irreversible degeneration occurs. Our approach is intended to address these significant limitations of HSCT.

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

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

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

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



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

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

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

Our strategy

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

- Continue our commercialization efforts for Libmeldy (OTL-200) for treatment of eligible patients with early-onset MLD in Europe and expand geographically into new markets as regulatory approvals are obtained
- Advance our clinical-stage product candidates towards marketing approvals, including a potential BLA submission for OTL-200 in the U.S. in mid-2023
- Leverage the power of our therapeutic approach to investigate the potential of HSC gene therapy in larger indications
- Invest in new technologies and innovations to continue to improve our manufacturing processes for lentiviral vector and drug product and reduce costs of goods manufactured
- Establish end-to-end process development, manufacturing and supply chain capabilities, initially through third parties and internally over time
- Establish a patient-centric, global commercial infrastructure, including with third parties in certain regions where we do not have a direct presence
- Execute a business development strategy to leverage our HSC gene therapy approach, expand geographically, accelerate time-to-market or attract disease-area expertise to optimize the value of our portfolio of product candidates or expand into new indications

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

Our pipeline

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

- Our programs focused on neurodegenerative disorders consist of our commercial program approved in Europe, Libmeldy (OTL-200) for MLD, two clinical proof of concept-stage programs, OTL-203 for MPS-I and OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, and one pre-clinical program, OTL-204 for frontotemporal dementia with progranulin mutations, or GRN-FTD.
- Our programs in immunological disorders consist of two pre-clinical programs, OTL-104 for Crohn's disease with mutations in the nucleotide-binding oligomerization domain-containing protein 2, or NOD2-CD, and OTL-105 for HAE.
    - In July 2021, we entered into a collaboration with Pharming Group N.V., or Pharming, pursuant to which we granted Pharming worldwide rights to OTL-105. Under our agreement with Pharming, we will lead the completion of IND-enabling activities of OTL-105 and oversee its manufacturing during pre-clinical and clinical development, which will be funded by Pharming. Pharming will be responsible for clinical development, regulatory filings and commercialization of OTL-105, if approved, including associated costs.

– We also have a commercial product approved in Europe, Strimvelis for ADA-SCID, an advanced registrational clinical program, OTL-103 for Wiskott Aldrich syndrome, or WAS, and one clinical proof of concept-stage program, OTL-102 for X-linked chronic granulomatous disease, or X-CGD. However, in March 2022, we announced that we would discontinue our investment in and seek alternatives for these programs.

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

Neurodegenerative Disorders

Gene therapy for treatment of MLD

Disease overview

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

Limitations of current therapies

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

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

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

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

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

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

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

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

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

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

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

Co-primary endpoints
The co-primary endpoints of the integrated efficacy analysis were Gross Motor Function Measure, or GMFM, total score and ARSA activity, both evaluated at two years post-treatment. Results of this analysis indicate that a single-dose intravenous administration of Libmeldy is effective in modifying the disease course of early-onset MLD in most patients.

Pre-symptomatic LI and EJ patients treated with Libmeldy experienced significantly less deterioration in motor function at two years and three years post-treatment, as measured by GMFM total score, compared to age and disease subtype-matched untreated patients ($p \leq 0.008$). The mean difference between treated pre-symptomatic LI patients and age-matched untreated LI patients was 71.0% at year 2 and 79.8% at year 3. Similarly, the mean difference between treated pre-symptomatic

EJ patients and age-matched untreated EJ patients was 52.4% at year 2 and 74.9% at year 3. Although not statistically significant, a clear difference in GMFM total score was also noted between treated early-symptomatic EJ patients and age-matched untreated EJ patients (28.7% at year 2; p=0.350 and 43.9% at year 3; p=0.054).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(1) Hurler, or MPS-IH, (2) Scheie, or MPS-IS (3) and Hurler-Scheie, or MPS-IH/S, syndromes. MPS-IH is the most severe form of MPS-I.

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

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

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

Despite its established position in treatment algorithms, allogeneic-HSCT can result in alloreactive complications, including and graft versus host disease or death, particularly when the degree of matching between graft donor and recipient is poor. Additionally, there remains a significant disease burden in those treated, even if treated early in life, including severely debilitating cognitive, neurological, growth, orthopedic, cardiac, respiratory and ophthalmic manifestations, all of which are reported during long-term post-HSCT follow-up.

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

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

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

One way in which OTL-203 differs from allo-HSCT is the ability of the transduced autologous cells to produce supraphysiological levels of IDUA enzyme in peripheral compartments and increased IDUA

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

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

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

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

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

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

In September 2022, we announced the presentation of the interim clinical results from the ongoing academic-sponsored clinical trial at the San Raffaele Hospital. For this presentation's last follow up of all patients (range: 24 and 36 months), interim data supporting clinical proof-of-concept illustrated that treatment with OTL-203 was generally well-tolerated with a safety profile consistent with the selected conditioning regimen. IDUA antibodies present prior to gene therapy as a result of ERT were not seen in any patient within three months following treatment. In addition, ERT was discontinued at least three weeks prior to any patient receiving gene therapy treatment, and no patients had re-started ERT post-treatment.

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

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

Gene therapy for treatment of MPS-IIIA

Disease overviews

MPS-IIIA, also known as Sanfilippo syndrome type A, is a life-threatening metabolic disease that causes accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within the first years after birth, MPS-IIIA and MPS-IIIB patients begin to experience progressive neurodevelopmental delay and decline, including speech delay and eventual loss of language, behavioral disturbances and potentially severe dementia. Ultimately, most patients with MPS-IIIA progress to a vegetative state. Life expectancy for patients with MPS-IIIA is between 10 to 25 years.

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

Limitations of current therapies

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

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

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

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

Proof of concept trial in MPS-IIIA

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

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

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

Treatment with OTL-201 was generally well-tolerated in the initial study population. Of the six serious adverse events (SAEs) reported to date, four were determined to be due to conditioning or leukapheresis and one was related to background disease. One patient had delayed platelet engraftment until day 52 post-treatment, likely due to Cytomegalovirus infection around the time of infusion.

Research program in FTD

Disease overview

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

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

Limitations of current therapies

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

Our solution, OTL-204 for treatment of FTD

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

Pre-clinical development of OTL-204

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

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

Immunological Disorders

Research program in NOD2-Crohn's Disease

Disease overview

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

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

Limitations of current therapies

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

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

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

Pre-clinical development of OTL-104

OTL-104 pre-clinical work has shown that restoration of NOD2 gene expression in murine and human stem cells can rescue a defective myeloid immune response to MDP. NOD2 defective inflammatory functions in primary human myeloid cells can be restored by both lentiviral and gene editing approaches. The OTL-104 lentiviral vector is designed to express NOD2 under the chimeric CathepsinG/cFES promoter to deliver myeloid directed transgene expression. Pre-clinical studies to evaluate the safety of this approach show that NOD2-LV gene modification of human $CD34^{+}$stem

cells and murine *lineage* negative stem cells does not affect HSC engraftment or immune subset development and differentiation following transplantation into NSG or NOD2-KO mice, respectively. Transplantation of NOD2-LV gene modified murine stem cells further demonstrates that HSC derived cells can efficiently migrate and reconstitute the myeloid cell compartments of intestinal tissue, restoring a normal biodistribution of NOD2 expression within the gut.

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

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

Future applications of our ex vivo autologous HSC gene therapy approach
We believe that our versatile *ex vivo* autologous HSC gene therapy approach has the potential to deliver promising gene therapies to patients across a broad range of diseases. Although our near-term focus is on delivering our commercial and clinical-stage gene therapies to patients suffering from several rare diseases described above, we believe we can leverage our significant research and development experience and partnerships with academic institutions to identify other diseases in our target areas, including neurodegenerative, immunological and blood disorders, where *ex vivo* gene therapy may have a comparably higher probability of success as compared to other approaches our mid- to long-term strategy is to leverage our HSC gene therapy approach in additional larger indications, seeking development partnerships as the programs advance towards the clinic. One partnership already established in 2021 is our collaboration with Pharming on OTL-105, as referenced above.

Our regulatory strategy

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

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

Manufacturing

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

Global supply network with experienced CDMOs

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

Manufacturing efficiencies and scalability

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

Cryopreservation of our gene therapy programs

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

approval in the United States and Europe. Our programs in OTL-203 and OTL-201 have already started or will start with cryopreserved formulations. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

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

Commercial operations

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

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

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

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

Intellectual property and barriers to entry

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

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

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

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

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment

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

License agreements

GSK asset purchase and license agreement

In April 2018, we entered into the GSK Agreement, pursuant to which GSK transferred its portfolio of approved and investigational rare disease gene therapies to us, which included Strimvelis and OTL-200 for MLD, among other programs. GSK also simultaneously novated to us their R&D Agreement with Telethon-OSR.

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

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

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. For example, for Libmeldy, we pay a tiered royalty rate at percentages from the mid-teens to the low twenties. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to OTL-200 may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048.

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

Telethon-OSR research and development collaboration and license agreement

In April 2018, in connection with our entering into the GSK Agreement, we entered into a deed of novation with GSK, Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, pursuant to which we acquired and assumed all of GSK's rights and obligations under the R&D Agreement with Telethon-OSR for the research, development and commercialization of *ex vivo* HSC gene therapies for certain programs, including OTL-200 and Strimvelis.

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

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

As consideration for the licenses and options granted under the R&D Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are obligated to pay up to an aggregate of €31.0 million in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement, including OTL-200. Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a

country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves a certain threshold percentage of the market share.

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

Oxford BioMedica license and development agreement

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

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

As consideration for the licenses granted under the agreement, we issued 588,220 of our ordinary shares to Oxford BioMedica. We are also obligated to issue additional equity upon the achievement of certain milestones, pursuant to which we issued 150,826 ordinary shares upon the achievement of the first milestone in November 2017 and 150,826 ordinary shares were issued upon the achievement of further milestones in August 2018. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica. Additionally, we are obligated to pay low

single-digit percentage royalties on net sales of licensed products until January 31, 2039. The foregoing royalties are reduced by a mid-double digit percentage in the case of compassionate use of a licensed product in a country until the first commercial sale following marketing authorization in such country. We are also required to pay a set monthly fee to Oxford BioMedica in the event we use a certain Oxford BioMedica system for generating stable cell lines.

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

Telethon-OSR license agreement

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

Competition

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

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

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

- **MLD**: To our knowledge, beyond Libmeldy in Europe, there is currently no other effective treatment option for patients with MLD. HSCT, for example, has demonstrated limited efficacy in halting disease progression and is therefore not considered a standard of care for this disease. A number of alternative approaches to HSCT are under investigation. For instance, Homology Medicines is at the pre-clinical stage of developing an *in vivo* AAV gene therapy for MLD delivered intravenously, Passage Bio has a pre-clinical development program for MLD, and Affinia has a pre-clinical program for *in vivo* AAV gene therapy for MLD through lumbar puncture (LP) administration. We are also aware that Takeda is investigating an ERT for MLD with a biweekly intrathecal infusion, and Denali Therapeutics is at the pre-clinical stage of developing a recombinant ARSA enzyme engineered to cross the blood-brain barrier.

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

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

Government regulation

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

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

U.S. biological products development process

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

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

- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA in accordance with any applicable expedited programs or designations;
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must

develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

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

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

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

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the CGTPs. These are FDA

regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through appropriate screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. During the COVID-19 pandemic, restrictions preventing the conduct or completion of facility or clinical site inspections have led to FDA deferred action on marketing applications or the issuance of complete response letters. To assure cGMP, CGTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

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

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

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

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a

drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

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

Rare Pediatric Disease Designation and Priority Review Vouchers

Under the FD&C Act, the FDA incentivizes the development of drugs and biological products that meet the definition of a "rare pediatric disease," defined to mean a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making in the United States a drug or biological product for such disease or condition will be received from sales in the United States of such drug or biological product. The sponsor of a product candidate for a rare pediatric disease may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug or biological product application after the date of approval of the rare pediatric disease drug or biological product, referred to as a priority review voucher, or PRV. A sponsor may request rare pediatric disease designation from the FDA prior to the submission of its BLA. A rare pediatric disease designation does not guarantee that a sponsor will receive a PRV upon approval of its BLA. Moreover, a sponsor who chooses not to submit a rare pediatric disease designation request may nonetheless receive a PRV upon approval of their marketing application if they request such a voucher in their original marketing application and meet all of the eligibility criteria. If a PRV is received, it may be sold or transferred an unlimited number of times. Congress has extended the PRV program through 30 September 2024, with the potential for PRVs to be granted through 30 September 2026.

Expedited development and review programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may help expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition

and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

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

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

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on an intermediate clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA is permitted to require, as appropriate, that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of accelerated approval was granted. FDORA also requires sponsors to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. FDORA also gives the FDA increased authority to withdraw approval of a drug or biologic granted accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit. Under FDORA, the FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress. In addition, for products being considered for accelerated approval, the FDA generally requires, unless otherwise informed by the agency, that all advertising and promotional materials intended for dissemination or publication within 120 days of marketing approval be submitted to the agency for review during the pre-approval review period.

RMAT designation

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

Post-approval requirements

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

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

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

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

U.S. patent term restoration and marketing exclusivity

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

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

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

Drug review and approval

In the EU, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products. Gene therapy products deliver genes into the body that lead to a therapeutic, prophylactic

or diagnostic effect. Libmeldy is authorized as a gene therapy product in the EU, and we anticipate that our gene therapy development products would also be regulated as ATMPs in the EU.

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

Now that the UK (which comprises Great Britain and Northern Ireland) has left the EU, Great Britain is no longer covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized marketing authorizations continue to be recognized in Northern Ireland). All medicinal products with an existing centralized marketing authorization were automatically converted to Great Britain marketing authorizations on 1 January 2021. For a period of three years from 1 January 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, could rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization. A separate application will, however, still be required. On 24 January 2023, the MHRA announced that a new international recognition framework will be put in place from 1 January 2024, which will have regard to decisions on the approval of marketing authorizations made by the European Medicines Agency and certain other regulators when determining an application for a new Great Britain marketing authorization.

Data and marketing exclusivity

The EU also provides opportunities for market exclusivity. Upon receiving a marketing authorization in the EU, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from referencing the innovator's pre-clinical and clinical trial data contained in the dossier

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

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

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

- a second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- the marketing authorization holder of the authorized orphan product consents to a second orphan medicinal product application; or

- the marketing authorization holder of the authorized orphan product cannot supply enough orphan medicinal product.

Since 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 marketing authorization. The criteria for orphan designation are the same as in the EU, save that they apply to Great Britain only (e.g., there must be no satisfactory method of diagnosis, prevention or treatment of the condition concerned in Great Britain, as opposed to the EU, and the prevalence of the condition must not be more than five in 10,000 persons in Great Britain).

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

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

development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

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

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

The aforementioned EU rules are generally applicable in the EEA.

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

Other healthcare laws and compliance requirements
In the United States, our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare

and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs may have to comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy and security provisions of the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, and similar state laws, each as amended, as applicable:

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

respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;

- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective 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 in May 2018. Following Brexit and the expiration of the subsequent transition period on 31 December 2020, the EU GDPR has been brought into UK law as the "UK GDPR" which, along with the UK Data Protection Act 2018, governs the collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the UK. In the present document, references to "GDPR" are meant to include both the EU GDPR and the UK GDPR, unless specified. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data.

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

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

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

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

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

Healthcare reform

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

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

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

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

Coverage and reimbursement

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

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

In addition, coverage and reimbursement for products can differ significantly from payor to payor. One payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree.

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

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

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

Key Performance Indicators (KPIs)

Management closely monitors cash position and runway. As of 31 December 2022, we had cash, cash equivalents, short-term investments, and restricted cash of $148.0 million down from $224.4 million in 2021. As a result of the Private Placement in March 2023 the Company received $34.0 million, this has extended the Group's cash runway into 2025. Our research and development expenses are also closely monitored and have decreased from $153.6 million in 2021 to $104.8 million in 2022. 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 the first quarter of 2022 we made our first commercial sale of Libmeldy. On March 30, 2022, the Company announced its commitment to focus on severe neurometabolic diseases and early research programs, and to discontinue its investment in and seek strategic alternatives for the Company's programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich syndrome ("WAS"), OTL-102 for treatment of X-linked chronic granulomatous disease ("X-CGD"), and Strimvelis for adenosine deaminase severe combined immunodeficiency ("ADA-SCID"). In the third quarter of 2022 we announced that the first confirmed case of a patient with metachromatic leukodystrophy (MLD) has been identified from the ARCHIMEDlife newborn screening (NBS) pilot study in collaboration with Hannover Screening Laboratory. In November 2022 we announced that we had secured clinical Type B meeting with U.S. FDA to take place in early 2023 prior to OTL-200 BLA submission.

Employees and Human Capital Resources

As of 31 December 2022 we had 166 full-time employees (2021: 250). We have no collective bargaining agreements with our employees, and we have not experienced any work stoppages. We consider our relationship with our employees to be positive. We monitor employee engagement through an annual survey and develop a prioritized action plan on an annual basis to address any areas in need of attention. Our human capital objectives include, as applicable, identifying, recruiting, developing, retaining, and incentivizing our existing and prospective employees, as well as optimizing the overall employee experience. The principal purposes of our incentive plans are to attract, retain and motivate our employees. The granting of share-based compensation awards is designed to reward selected employees for long-term shareholder value creation and our cash-based performance bonus awards reward the achievement of annual performance goals. The health and safety of our employees, customers and communities are of primary concern. During the COVID-19 pandemic, we have taken significant steps to protect our workforce, including, but not limited to, implementing a hybrid work model and social distancing protocols consistent with guidelines issued by federal, state and local laws.

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.
- Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.
- The results from our clinical trials for any of our product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. Before we submit our product candidates for marketing approval, the U.S. Food and Drug Administration or the European Medicines Agency may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.
- Interim data and ad hoc analyses are preliminary in nature. Success in pre-clinical studies or early clinical trials may not be indicative of results obtained in later trials.
- Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience, and we rely on third-party manufacturers that are often our single source of supply.
- Libmeldy™, Strimvelis® and our product candidates and the process for administering Libmeldy, Strimvelis and our product candidates may cause serious or undesirable side effects or adverse events.
- We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.
- We may be unable to establish effective sales and marketing capabilities, which would negatively impact our revenue.
- If the size and value of the market opportunities for our commercial products or product candidates are smaller than our estimates, or if we have difficulty in finding patients that meet eligibility requirements for Libmeldy or any of our product candidates, if approved, our product revenues may be adversely affected.

- We face significant competition in our industry and there can be no assurance that our commercial products or our product candidates, if approved, will achieve acceptance in the market.
- We may be unable to protect our intellectual property rights throughout the world.
- We may become subject to claims that we are infringing certain third-party patents.
- We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialize product candidates. These collaborations may not be successful.
- The market price of our ADSs may be highly volatile and may fluctuate due to factors beyond our control.

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 2022 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".

	2022	2021
Estimated greenhouse gas emissions from purchased electricity, heat, steam, or cooling for our own use (tCO^2e)	61.1	64.6
Underlying global energy use ('000 kWh)	304	316
Proportion of emissions related to the UK	37%	59%
Intensity ratio: Total greenhouse gas emissions per employee on the basis of a monthly average of 204 full-time equivalent employees (2021: 238)	0.30	0.27

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 remained roughly constant as we remained a primarily remote workforce. During 2022 we moved premises to new offices and laboratories in Hammersmith, London, during which we focused on choosing energy efficient options to reduce our future emissions.

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 2022 and 2021 is as follows:

31 December 2022:

	Male	Female	Total
Company Directors	6	2	8
Executives/Vice Presidents	14	5	19
Other Employees	58	89	147
Total Employees	78	96	174

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

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 18). 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 62) and "Diversity" (page 64) 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 board has had regard to the following matters:	More information
– 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 62).
– the impact of the Company's operations on the community and the environment;	Refer to the "Employees and Human Capital Resources" (page 62), "Diversity" (page 64), and "Information on Environmental Matters" (page 63) sections of this UK Statutory Strategic Report.
– the desirability of the Company maintaining a reputation for high standards of business conduct;	The Board sets high standards for the Company's employees, officers and Directors. Implicit in this philosophy is the importance of sound corporate governance. The Group has established a Code of Business Conduct and Ethics (the "Code"), which is posted in the Corporate Governance section of the Group's website and includes mechanisms for reporting suspected violations of the Code and other policies and procedures of the Company. The Company's employees, officers and Directors must review the Code periodically and are required to comply with its terms.
– The 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 27 April 2023 and signed on behalf of the Board of Directors by:

Hubert Gaspar
Director

27 April 2023

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 2022. 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 17 of this Annual Report.

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 $104.8 million (2021: $153.6 million).

Results and dividends
The Company's consolidated financial results for the year are set out on page 102 of this Annual Report. For the year ended 2022 the Directors do not recommend the payment of a dividend (2021: 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 23 to the consolidated financial statements. Share capital activity for the 2022 financial year is outlined on page 105 of the consolidated financial statements in the Consolidated statement of changes in equity.

Political Contributions
No political donations were made, and no political expenditure was incurred, by the Company, during 2022 (2021: nil).

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

Issuance of shares through 2023 Private Placement
On 6 March 2023, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") pursuant to which the Company agreed to sell, in an unregistered offering, up to an

aggregate of (i) 99,166,900 shares, consisting of a combination of Ordinary Shares, nominal value £0.10 per share ("Ordinary Shares") and Non-Voting Ordinary Shares, nominal value £0.10 per share ("Non-Voting Ordinary Shares" and together with the Ordinary Shares, "Shares") and (ii) warrants to purchase an aggregate of 109,083,590 Ordinary Shares or Non-Voting Ordinary Shares (the "Warrants").

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

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

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

The second closing is expected to occur on the fifth trading day after the Company notifies the purchasing parties that the Second Closing Trigger has occurred and is subject to additional, customary closing conditions. If the Second Closing Trigger occurs, the Company anticipates receiving gross proceeds of approximately $34.0 million from the second closing of the 2023 Private Placement, before deducting fees to the placement agent and other offering expenses payable by the Company.

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

Going Concern
The Group expects that its cash, cash equivalents, and short-term investments as of 31 December 2022, of $143.8 million, together with expected proceeds from sales of Libmeldy and the $34 million received in March 2023 from the 2023 Private Placement, will be sufficient to fund its operations and capital expenditure requirements for at least twelve months from the date of signing of this Annual Report and Financial Statements. Management have prepared a budget to support the going concern assumption of the Group which shows the Group has sufficient resources to continue as a going concern into 2025. 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 62 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 63 of this Annual Report.

Financial Risk Management
Credit and Interest Rate Risk
As of 31 December 2022, we had cash, cash equivalents, short-term investments, and restricted cash of $148.0 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying UK and U.S. bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We have borrowed $33.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 5.95% plus LIBOR. As of 31 December 2022, the carrying value of the term loans under the credit facility was $32.4 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. 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). As at 31 December 2022, our credit facilities reference LIBOR-based rates. In January 2023, we amended and restated our credit facility to change from LIBOR to SOFR. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

Liquidity Risk
From our inception through 31 December 2022, we have not generated significant revenue from product sales and incurred significant operating losses and negative cash flows from our operations.

We acquired our commercial product Strimvelis and the program that is now Libmeldy from GSK in April 2018, and our product candidates are in various phases of preclinical and clinical development. In December 2020, the European Commission granted standard marketing authorization for Libmeldy. We launched Libmeldy in Europe and generated product revenue during the year ended 31 December 2022. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our IPO and follow-on offering, proceeds from the sale of ordinary shares in our private placement, proceeds from the sale of convertible preferred shares, reimbursements associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program, reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., our Original Credit Facility and our Amended Credit Facility with MidCap, and through proceeds from sales of Libmeldy in Europe beginning in 2022.

On 27 February 2020, we entered into a Sales Agreement with Cowen and Company, LLC ("Cowen"), as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. On 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. On 6 October 2022 we entered into a Sales Agreement with Guggenheim Securities, LLC, as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $30.0 million. As of 31 December 2022, we have not sold any shares under the Guggenheim 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 in the Notes to the Consolidated financial statements.

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. We recorded realized and unrealized foreign currency losses of $24.3million in the year to 31 December 2022 (2021: $1.1million loss). 2022 saw a significant change in the U.S. dollar to GB pound exchange rate, with the rate changing by 12%. There are significant intercompany loans between Group companies that are denominated in U.S. dollars where the functional currency of the counterparty company is in GB pounds. The change in exchange rate resulted in large foreign currency losses on these balances. These foreign currency transaction gains and losses are included in the Consolidated statement of profit and loss.

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
Orchard Therapeutics (Sweden) AB	Sweden

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

27 April 2023

DIRECTORS' REMUNERATION REPORT

Annual Statement from the Chair of the Compensation Committee

Dear Shareholder,

As the Chair of the Compensation Committee (the "Committee"), I am pleased to present, on behalf of the Board of Directors (the "Board") of Orchard Therapeutics plc (the "Company" or "Orchard"), the Directors' Remuneration Report for the year ended 31 December 2022 (the "Remuneration Report").

The Company's Remuneration Report will be subject to an advisory vote at the forthcoming Annual General Meeting on 14 June 2023 (the "AGM").

Introduction

Our executive compensation program seeks to incentivize and reward strong corporate performance. All compensation decisions at Orchard remain aligned to our key principle of paying for performance. Further, as a global biopharmaceutical company with major operations in the United States and Europe we operate within a global marketplace for talent. Given that the market for experienced directors and biopharmaceutical executive talent is very competitive, particularly in the United States, the Committee references the U.S. 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, we were pleased to receive shareholder support adopting our 2022 Remuneration Policy at the 2022 AGM. Gratefully supported by our shareholders, 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.

Key remuneration decisions for 2022

The Committee and I were mindful of the prevailing economic environment, fiscal position and available cash resources of the Company at year-end 2022 and the Company's share price performance during the year. We acknowledge and celebrate the many achievements made by all our colleagues at Orchard while ensuring the broader context of the Company and the macro-economic environment are considered when making remuneration decisions.

In the first quarter of 2022, all employees' salaries at Orchard were increased by 5%. This decision was made in response to the competitive landscape of the biotechnology sector and a fast-paced compensation market for talent and skills we require as well as the inflationary environment in which we are operating. The CEO's salary was treated in the same manner as all other employees.

Two key decisions during 2022 related to equity-based compensation. Firstly, to reinforce the performance focus of our executive compensation program, the CEO's annual equity award, half of the award was granted as performance-based share options with an exercise price set at a 25% premium above the share price on the date of grant.

Secondly, in October 2022 and under the terms of the Company's Share Option Incentive Plan 2018, the Board of Directors approved a repricing of previously awarded share options which were significantly 'underwater'. In the situation where substantial portions of employees' equity holding had little or no value, the Board took the decision to reprice these awards. This was done in order to reengage staff with the future success of Orchard and provide additional retentive value to the investment previously made in our equity program. The Company has, and continues to grant, equity-based compensation to all employees – aligning the entire workforce with the future value of the Company. The CEO's equity was treated in the same manner as all other employees, with details shown in the Annual Report on Remuneration. In making this decision, the Board of Directors considered several factors in determining which grants would be eligible for repricing and which grants would remain on the original terms, including (i) none of the non-executive director grants were repriced; (ii) only grants with an original exercise price above $1.25[1] were repriced, representing a 150% premium to the share price on the date of repricing; (iii) none of the grants from 2022 were repriced; and (iv) the exercise price of the repriced options was set at a 16% premium to the closing market price on the date of repricing.

2022 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 2022 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 and consistent for all employees, the Committee determined a corporate score of 85% of target. This is reflective of the Company as a whole making considerable strides towards all of our stated objectives while also acknowledging that some key objectives were not achieved during the year due to either internal or external factors. The Committee does however recognize that the progress and achievements during 2022 puts the Company in a favorable position with considerable momentum going into 2023 and beyond.

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 2023

There are no substantial changes to our approach to executive compensation for 2023. At his own request and recommendation, the CEO will not receive a salary increase for 2023. The Committee commends Dr. Gaspar for this proposal.

Consistent with our pay for performance philosophy, we continue to make an annual award of share options to Dr. Gaspar for 2023. Consistent with 2022, we have granted half of the 2023 award in performance-based, premium-priced options – options with an exercise price above the stock price on the date of grant. This instills a further hurdle before a portion of Dr. Gaspar's long-term incentive has any intrinsic value and further aligns our compensation approach with the shareholder experience. Similarly, a portion of the 2023 options granted to the entire executive team were also issued with an exercise price at a premium above the stock price on the date of grant.

1 Share price before 1:10 American Deposit Share (ADS) ratio change effective on 10 March 2023.

As part of an on-going review of the Board's remuneration, an adjustment to the fees paid to Non-Executive Directors will be implemented for 2023. The principal adjustment is the reduction by $5,000 in the base cash compensation provided for Board membership – this removes a supplement previously provided for time and commitment to international travel with a corresponding rebalancing in equity compensation. Additionally, from 2023 a shareholding guideline of three-times this base fee is introduced for Non-Executive Directors with a five year period allowed for each Board member to gain compliance. We believe this is an important step in reinforcing the connection between the Board and the long-term value of the Company.

Conclusion

The Committee believes that the Directors' Remuneration Policy has been implemented fairly and consistently, as described in this report. We are confident that remuneration arrangements will continue to properly motivate our Directors and executive team 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

27 April 2023

Remuneration Policy

The following section sets out our Directors' Remuneration Policy (the "Policy") as approved by binding shareholder vote at the annual general meeting on 7 June 2022. The document, as approved, can be found in the Company's 2021 Annual Report.

The policy received strong shareholder support, as has the implementation of the policy in the annual voting.

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 2023, 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.

An illustration of the application of the Remuneration Policy can be found in the Company's 2021 Annual Report.

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 of 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 2022 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 31.12.22
Joanne Beck	1 July 2018	4 years 6 months
Marc Dunoyer	6 June 2018	4 years 7 months
James Geraghty	4 June 2018	4 years 7 months
Charles Rowland	1 June 2018	4 years 7 months
Alicia Secor	7 December 2018	4 years 1 month
John Curnutte	30 August 2019	3 years 4 months
Steven Altschuler	3 February 2020	2 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.

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"). 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 14 June 2023.

Compensation Committee (the "Committee")

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

The Chairman of the Board 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 in consultation with our independent compensation consultant.

Meetings attendance during 2022

	Attendance
Charles Rowland	5 of 5
Joanne Beck, Ph.D.	5 of 5
Alicia Secor	5 of 5

Independent advisors

Each year the Committee appoints a wholly independent advisor to provide advise on executive and board remuneration. For 2022, the Committee reappointed the Executive Compensation practice of Aon plc. Aon advises on remuneration arrangements and all aspects of senior executive and board remuneration. In 2022, Aon assisted the Committee and kept the Committee up to date on remuneration trends and regulations. During the 2022 financial year, fees charged by Aon for advice provided to the Committee amounted to $115,943 (2021: $131,226) (excluding VAT) on a time and materials basis. In addition, Aon provided advice to the Company's Human Resources function on implementation of HR initiatives. The Company's retained external legal counsel, Goodwin Procter LLP have also advised the Committee and the Company's Human Resources function on compensation. The Committee reviews the independence of all external advisors on an annual basis and considers that additional services by Aon and Goodwin in no way prejudices their position as independent advisors to the Committee.

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 incentivized 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 or other countries in which the Company operates;
- reviewing, evaluating, and approving employment agreements, severance agreements, change-of-control protections, equity grants, corporate performance goals and objectives, and other compensatory arrangements of the executive officers and other senior management and adjusting remuneration, as appropriate;
- evaluating and approving remuneration plans and programs and establishing equity remuneration policies;
- reviewing remuneration practices and trends to assess the adequacy and competitiveness of the executive remuneration programs as compared to industry peers, and determining the appropriate levels and types of remuneration to be paid;
- approving any loans by the Company to employees;
- reviewing and approving remuneration arrangements for any executive officer involving any subsidiary, special purpose or similar entity, with consideration of the potential for conflicts of interest; and
- reviewing the Company's practices and policies of employee remuneration as they relate to risk management and risk-taking incentives.

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

Statement of shareholder voting at 2022 AGM

At last year's AGM held on 7 June 2022, 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	93.4%	48,023,460	6.3%	3,247,147	0.3%	150,066
To approve the Directors' Remuneration Policy	93.3%	47,965,263	6.5%	3,334,672	0.2%	120,738

Single total figure of Directors' remuneration – year ended 31 December 2022 (audited)

The total remuneration of the individual Directors who served in the year ended 31 December 2022, 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	Total remun-eration $000	Total fixed	Total variable
Executive Directors									
Bobby Gaspar[1]	2022	572.7	4.0	37.8	294.4	–	908.9	614.5	294.4
	2021	605.1	3.2	27.2	217.8	–	853.3	635.5	217.8

		Base salary /fees $000	Benefits[2] $000	Pension $000	Bonus $000	SOIP[3] $000	Total remun-eration $000	Total fixed	Total variable
Non-Executive Directors									
Steven Altschuler	2022	52.7	–	–	–	–	52.7	52.7	–
	2021	51.9	–	–	–	–	51.9	51.9	–
Joanne Beck	2022	60.2					60.2	60.2	–
	2021	59.4	–	–	–	–	59.4	59.4	–
John Curnutte	2022	60.2					60.2	60.2	–
	2021	63.7	–	–	–	–	63.7	63.7	–
Marc Dunoyer	2022	59.2					59.2	59.2	–
	2021	59.1	–	–	–	–	59.1	59.1	–
James Geraghty	2022	95.4					95.4	95.4	–
	2021	95.1	–	–	–	–	95.1	95.1	–
Charles Rowland	2022	82.8					82.8	82.8	–
	2021	78.1	–	–	–	–	78.1	78.1	–
Alicia Secor[5]	2022	66.8					66.8	66.8	–
	2021	72.1	–	–	–	–	72.1	72.1	–
Total	2022	1050.0	4.0	37.8	294.4	0.0	1386.2	1091.8	294.4
	2021	1084.6	3.2	27.2	217.8	0.0	1332.7	1114.9	217.8

1. Dr. Gaspar's salary is £462,000 per annum, which increased by 5% from £440,000 effective 1 March 2022. 2022 figures are converted at a 12-month average rate for 2022 of GBP 1 = USD 1.2495. 2021 figures are converted at a 12-month average rate for 2021 of GBP 1 = USD 1.3753. Due to exchange rate fluctuation, the 2022 salary increase does not correspond to an increased reporting amount in USD.
2. For Executive Directors, benefits include 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 Share Option Incentive Plan (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. 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.

2022 Annual bonus

During a series of meetings between December 2022 and February 2023, the Compensation Committee evaluated the achievement of the 2022 corporate objectives and the Chief Executive's individual performance.

The Compensation Committee reviewed the corporate goals, below, and based on the results, approved an 85% achievement level of the 2022 corporate objectives.

Successes during 2022 spanned across all areas of the Company's activity, each individually and collectively critical for the long-term success of the Company. Overcoming a number of challenges in the year, the achievements assessed by the Committee have built considerable momentum for the Company across our portfolio and business operations.

Key achievements against agreed goals include those from commercial, regulatory, clinical- & pre-clinical research as well as financial. These are:

i. extending the Company's cash runway through portfolio prioritization, expense management, new capital and business development;

ii. driving net revenue from Libmeldy sales;

iii. advancing our portfolio to key clinical and regulatory milestones;

iv. strategic decisions in pre-clinical research activities, notably relating to Crohn's disease.

A series of scientific and business-related achievements during the year were also noted by the Committee in approving the achievement for the year.

Annual Bonus (audited)
As CEO, Dr Gaspar's annual bonus is directly linked to the performance of the Company. A Corporate Performance Score of 85% therefore corresponds to a bonus outcome equivalent to 85% of target for the CEO. This equates to a 2022 bonus payment equal to 51% of his base salary.

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

Executive Director	Base salary ($)	Target Annual Cash Bonus (% of salary)	Corporate performance	Cash payment % salary	Cash outcome ($)
Bobby Gaspar	$577,250	60%	85%	51%	$294,397

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 1.2495, which was the average rate during 2022. The salary basis for the bonus was Dr Gaspar's salary as CEO, £462,000.

Share Option Incentive Plan

Awards granted to Executive Directors in 2022 (audited)

During 2022, Dr Gaspar was granted an annual equity award. This award was made as an award of share options, split into two tranches:

– options with an exercise price set at the Company's closing share price on the date of grant ('market-priced' options); and

– options with an exercise price set at a 25% premium to the Company's closing share price on the date of grant ('premium-priced' options).

The Committee believes that granting share options to the CEO remains the most effective alignment between executive compensation and long-term shareholder interest. The addition of premium-priced options during 2022 reinforces this alignment and ensures that a substantial portion of Dr Gaspar's compensation package is contingent on long-term and sustainable value growth of the Company.

Executive Director	Form of Award	Date of Grant	Shares Covered[1]	Exercise Price[1]	Face Value at Date of Grant[2]	Fair Value at Date of Grant[2]	Expiry Date	Vested in 2022[3]	Exercised	Value realized at exercise or vesting	Un-vested
Bobby Gaspar	Market-priced Options	1 June 2022	422,631	$0.4591	$194,030	$126,844	31 May 2032	88,048	nil	n/a	334,583
Bobby Gaspar	Premium-priced Options	1 June 2022	427,369	$0.57388	$196,205	$120,094	31 May 2032	89,035	nil	n/a	338,334

1 The numbers of share and share prices are before the 1:10 American Deposit Share (ADS) ratio change which became effective on 10 March 2023.
2 Market-priced 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 the date of grant is calculated as the Black Scholes value. The face value of the premium-priced options is the number of shares covered multiplied by the share price on the date of grant.
3 The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the vesting commencement date of 1 February 2022.

In October 2022 under the terms of Orchard's Share Option Incentive Plan 2018 the Board of Directors approved a repricing of previously awarded share options to employees which were significantly 'underwater' i.e., where the exercise prices were significantly above the Company's recent trading price. This repricing took effect on October 4, 2022.

All employees at the Company hold share options and in the situation where substantial portions of employees' equity holding had little or no value, the Board took the decision to reprice these awards. This was done in order to reengage staff with the future success of Orchard and provide additional retentive value to the investment previously made in our equity program. The Company has, and continues to grant, equity-based compensation to all employees – aligning the entire workforce with the future value of the Company.

The Board of Directors considered several factors in determining which grants would be eligible for repricing and which grants would remain on the original terms:

- None of the non-executive director grants were repriced;
- Only grants with an original exercise price above $1.25 were repriced, representing a 150% premium to the price on the date of repricing;
- None of the grants from 2022 were repriced; and
- The exercise price of the repriced options ($0.58) was set at a 16% premium to the closing market price on the date of repricing ($0.50).

As CEO, Dr Gaspar's awards were treated in the same manner as all other employees. Awards granted to Dr Gaspar during 2019, 2020 and 2021 were therefore impacted by this action, with a repriced exercise price for the awards listed below set at a premium of 16% above the Company's closing share price of $0.50 on 4 October 2022.

Executive Director	Form of Award	Date of Grant	Shares Covered[1]	Exercise Price on Date of Grant	Exercise Price[1]	Face Value at Date of Grant	Face Value on 4 October 2022	Expiry Date	Vested at 31.12.22	Exercised	Un-vested
Bobby Gaspar	Market-price options	16 January 2019	50,000	$12.54	$0.58	$627,000	$29,000	15 January 2029	48,958[2]	nil	1,042
	Market-price options	2 January 2020	200,000	$13.58	$0.58	$2,716,000	$116,000	1 January 2030	145,833[2]	nil	54,167
	Market-price options	1 April 2020	300,000	$7.05	$0.58	$2,115,000	$174,000	31 March 2030	200,000[2]	nil	100,000
	Market-price options	1 February 2021	850,000	$5.98	$0.58	$5,083,000	$493,000	31 January 2031	389,583[2]	nil	460,417
	Market-price options	1 February 2021	55,006	$5.98	$0.58	$328,936	$31,903	31 January 2031	55,006[3]	nil	n/a

1 The numbers of shares and share prices are before the ADS ratio change which became effective on 10 March 2023.
2 The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the date of grant.
3 These options vested in equal monthly tranches over 12 months.

Awards granted to Non-Executive directors between 1 January 2022 and 31 December 2022 (audited)

Non-executive directors received the following option awards during the year, each vesting based on continued service only.

Non-Executive Directors	Form of Award	Date of Grant	Shares Covered[1]	Exercise Price[1]	Face Value at Date of Grant[1]	Fair Value at Date of Grant[1]	Expiry Date	Vested[1]	Exercised	Value realized at exercise	Un-exercised
Steven Altschuler	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000
Joanne Beck	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000
Marc Dunoyer	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000
James Geraghty	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000
Charles Rowland	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000
Alicia Secor	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000
John Curnutte	FMV Options*	7-Jun-22	46,000	$0.47	$21,836	$13,880	6-Jun-32	nil	nil	nil	46,000

1 The numbers of shares and share prices are before the ADS ratio change which became effective on 10 March 2023.
2 The fair market value options are granted at the market price which is the exercise price. The face value at date of grant is calculated as the number of shares multiplied by the exercise price. The fair value at date of grant is calculated as the Black Scholes value.
3 The options vest and become exercisable at the earlier of one year from the date of grant or the next AGM.

Payments for loss of office (audited)

No payments were made for loss of office to Directors 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 of 31 December 2022 (together with interests held by his or her connected persons) are set out in the table below.

During 2022 the Compensation Committee implemented formal shareholding requirements for Executive Directors. 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 meet or exceed this guideline within 5 years of appointment or 5 years from the implementation of this requirement.

From 2023, a shareholding requirement will be extended to the full Board of Directors and the other Executive Officers of the Company.

			Restricted Shares		Share Options		
	Beneficially owned shares as at 31/12/22	% Salary held	Unvested without performance conditions	Unvested with performance conditions	Vested but unexercised	Unvested without performance conditions	Unvested with performance conditions
Executive Directors							
Bobby Gaspar	370,158	24%[1]	–	195,000[2]	1,750,765	950,209	338,334[3]
Non-Executive Directors							
Steven Altschuler	–	n/a	–	–	122,222	48,778	–
Joanne Beck	9,292	n/a	–	–	190,030	46,000	–
John Curnutte	–	n/a	–	–	125,000	46,000	–
Marc Dunoyer	37,179	n/a	–	–	190,030	46,000	–
James Geraghty	44,391	n/a	–	–	430,120	46,000	–
Charles Rowland	12,294	n/a	–	–	190,030	46,000	–
Alicia Secor	–	n/a	–	–	160,000	46,000	–

1 The value of Dr. Gaspar's beneficially owned shares is calculated using the closing price of Orchard's shares on 31 December 2022. As the CEO, Dr. Gaspar has a shareholding requirement of 5x base salary and has until 2027 to achieve this following the implementation of this requirement in 2022. The Committee notes Dr. Gaspar's vested and unvested holdings.

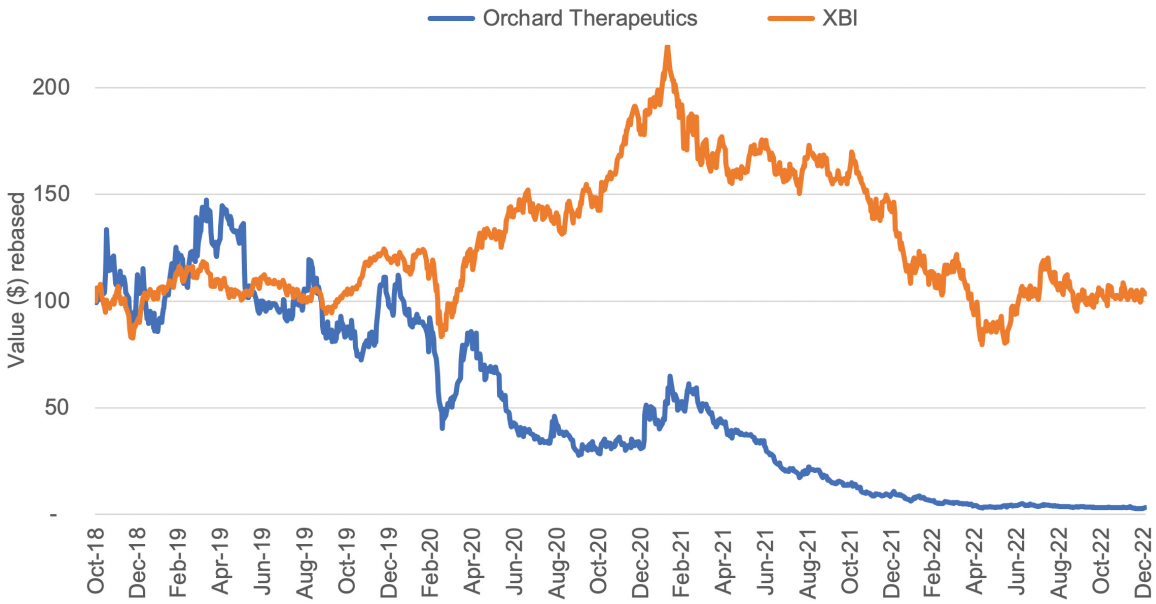
2 Refers to a one-time grant of Performance Share Units (PSUs) awarded to Dr. Gaspar on 1 April 2020. This PSU award vests as follows: 1/3 of the PSUs will vest on each of the first three of specific clinical and regulatory milestones achieved, subject to Bobby Gaspar remaining an employee of the Company on the date of achievement and provided that in each case the milestone is achieved on or before 2 January 2024. None of these awards have vested. The specific milestones are considered commercially sensitive. Details of the milestones and performance against them will be disclosed at the appropriate time.

3 In 2022 Dr. Gaspar was awarded share options with an exercise price set at a 25% premium to the market price on the date of grant.

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 2022. 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 2022, 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	2022
Total remuneration ($000)[1]	$555	$1,016	$764	$853	$909
Actual bonus (% of the maximum)[2]	N/A	44.0%	37.5%	22.5%	31.8%
SOIP vesting (% of the maximum)[3]	N/A	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. These figures are also impacted by exchange rate fluctuations between the currency in which Dr. Gaspar is paid, GBP, and our reporting currency, USD.
2 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.
3 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 recognized 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.

	2021	2022	% change
Total operating expenses ($'000)	$206.8	$174.9	-15.4%
Total employee pay expenditure ($'000)[1]	$71.1	$61.5	-13.5%

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 $11,418k and $19,900k in non-cash share-based compensation expense for 2022 and 2021 respectively.

Average percentage change in remuneration of Directors and Employees

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 2022.

	Change in pay between 31/12/2021 and 31/12/2022			Change in pay between 31/12/2020 and 31/12/2021			Change in pay between 31/12/2019 and 31/12/2020		
	Base salary/fee	Bonus	Benefit	Base salary/fee	Bonus	Benefit	Base salary/fee	Bonus	Benefit
Executive Directors									
Bobby Gaspar[1]	-5%	35%	38%[2]	12%	28%[3]	361%[2]	58%	-54%	0%
Non-Executive Directors[4]									
Steven Altschuler	1%	n/a	n/a	10%	n/a	n/a	n/a[5]	n/a	n/a
Joanne Beck	1%	n/a	n/a	2%	n/a	n/a	41%	n/a	n/a
John Curnutte	-5%	n/a	n/a	5%	n/a	n/a	278%[6]	n/a	n/a
Marc Dunoyer	0%	n/a	n/a	-1%	n/a	n/a	27%	n/a	n/a
James Geraghty	0%	n/a	n/a	-1%	n/a	n/a	15%	n/a	n/a
Charles Rowland	6%	n/a	n/a	-1%	n/a	n/a	31%	n/a	n/a
Alicia Secor	-7%	n/a	n/a	36%[7]	n/a	n/a	23%	n/a	n/a
Average employee[8]	n/a	n/a	n/a	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 received a 5% salary increase, in GBP, effective1 March 2022. He did not receive a salary increase in 2021 for his services as CEO. The increases represented here correspond to a salary increase upon promotion to CEO during 2020. These figures are also impacted by exchange rate fluctuations.

2 Dr. Gaspar's company-provided benefits are unchanged year-on-year – the reported figure combines the taxable value of private medical insurance and a cash allowance in lieu of pension. The 2021 increase relates to a cash allowance in lieu of pension contribution effective 1 April 2021 which he had not received prior to that date.

3 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.

4 None of the Non-Executive Directors are eligible for an annual bonus and none claimed any benefits during the year.

5 Steven Altschuler joined the Board during 2020 and therefore no comparative information is shown.

6 John Curnutte joined the Board in 2019 and the remuneration received in 2019 was not a full annual amount.

7 Alicia Secor received 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 As the parent company Orchard Therapeutics Plc has no direct employees. All employees are employed by the relevant legal entities.

Statement of implementation of remuneration policy in 2023

Annual base salary

At his own request, the Committee reviewed and commended a proposal from Dr Gaspar that his salary not be adjusted for 2023. Dr Gaspar recognized the prevailing economic environment, fiscal position and available cash resources of the Company at year-end 2022. Based on the combination of these factors he, therefore, did not wish to receive a salary increase.

	Base salary 2023	Base salary 2022 (from 1 March 2022)	% change
Bobby Gaspar, Chief Executive Officer	£462,000	£462,000	nil

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 at the Company, 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 2023 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 150% 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. The Executive Directors currently have no such arrangements in place.

Share Option Incentive Plan (SOIP)

Annual award of share options

In 2023, as part of the annual compensation package the CEO has been awarded an award of market-price and premium-price options in the Company at the same time as all eligible employees.

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 National Select Market on the date of grant. Consequently, approximately half of the CEO's 2023 share option award will have no intrinsic value until the share price increases by at least 25%.

The Committee believes that granting share options to the CEO remains the most effective alignment between executive compensation and long-term shareholder interest. The addition of premium-priced options since 2022 reinforces this alignment and ensures that a substantial portion of Dr Gaspar's compensation package is performance-based and contingent on long-term and sustainable value growth of the Company.

Executive Director	Form of Award	Date of Grant	Maximum Shares Covered	Exercise Price	Vest Terms
Bobby Gaspar	Market-priced share options	1 March 2023	563,410	$0.4636	(1)
	Premium-priced share options	1 March 2023	581,590	$0.5795	(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 2023

Non-Executive Directors are eligible to receive the following cash compensation annually. Following a review of the fees paid to the Board, the Company resolved to reduce by $5,000 the base fee provided to the Chair and Members of the Board. This removes a supplement previously provided for time and commitment to international travel with a corresponding rebalancing in equity compensation.

Additionally, the fee for the Chair of the Science and Technology Committee has been increased, recognizing the crucial role this position holds in the long-term success of the Company.

In reinforcing the Board's stewardship of the Company, from 2023, all Non-Executive Directors will be required to build up a shareholding equivalent to three times the base fee and they will have five years to gain compliance with this new requirement.

Collectively, the Compensation Committee believes these are important changes and represent incremental improvements to the Company's Board remuneration structure. The changes ensure that this structure matches long-term shareholder interest and remains market competitive.

	2023 Fee in $'000	2022 Fee in $'000
Base fee:		
Board Chair	$80	$85
Board Member	$40	$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	$15	$10
Science and Technology Committee Member	$7.5	$7.5

The Company intends to provide an initial, one-time equity award of 180,000 stock options (equivalent to 18,000 ADS following the 1:10 ratio change implemented on 10 March 2023) 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 105,000 stock options (equivalent to 10,500 ADS from 10 March 2023) to each Non-Executive Director at the 2023 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.

As approved in our 2022 Directors' Remuneration Policy Non-Executive Directors may 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 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 his own.

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

27 April 2023

ORCHARD THERAPEUTICS PLC
ANNUAL REPORT AND FINANCIAL STATEMENTS
31 DECEMBER 2022

Registered number 11494381

Consolidated Statement of Profit or Loss

for the year ended 31 December 2022

	Note	2022 $000	2021 $000
Product sales	3	**20,610**	700
Collaboration revenue	3	**2,045**	975
Total revenue	3	**22,655**	1,675
Cost of sales		**(6,771)**	(226)
Gross profit		**15,884**	1,449
Research and development expenses		**(104,833)**	(153,645)
Selling, general and administrative expenses		**(45,809)**	(51,847)
Other operating income and expenses	5	**(67)**	(90)
Net foreign exchange loss	5	**(24,344)**	(1,148)
Operating loss		**(159,169)**	(205,281)
Finance income	9	**2,580**	1,469
Finance expense	9	**(5,339)**	(5,799)
Net finance expense		**(2,759)**	(4,330)
Loss before taxation		**(161,928)**	(209,611)
Taxation	10	**8,058**	11,336
Loss for the year attributable to ordinary shareholders		**(153,870)**	(198,275)
Basic and diluted earnings per share ($)	6	**(1.20)**	(1.60)

Consolidated Statement of Comprehensive Loss

for the year ended 31 December 2022

	2022 $000	2021 $000
Loss for the year	**(153,870)**	(198,275)
Items that are or may be reclassified subsequently to statement of profit or loss:		
Foreign currency translation differences – foreign operations	**17,062**	1,097
Net change in fair value of debt investments at fair value through other comprehensive income	**(66)**	(251)
Other comprehensive loss for the year, net of income tax	**16,996**	846
Total comprehensive loss for the year	**(136,874)**	(197,429)

Consolidated Statement of Financial Position

As at 31 December 2022

	Note	2022 $000	2021 $000
Non-current assets			
Property, plant and equipment	12	**8,138**	4,767
Right-of-use assets	25	**12,769**	13,873
Intangible assets	13	**48,292**	63,408
Finance lease receivables	25	**12,905**	14,200
Other receivables	17	**5,725**	6,363
Deferred tax assets	11	**5,483**	3,113
		93,312	105,724
Current assets			
Inventories	16	**3,398**	2,015
Finance lease receivables	25	**1,294**	1,143
Trade and other receivables	17	**14,948**	22,435
Research and development tax credit receivable		**5,942**	30,723
Short-term investments	15	**75,326**	164,195
Cash and cash equivalents	18	**68,424**	55,912
		169,332	276,423
Total assets		**262,644**	382,147
Current liabilities			
Trade and other payables	20	**40,331**	33,655
Loans and borrowings	19	**9,429**	786
Lease liabilities	19	**6,424**	7,335
Deferred income	3	**959**	346
Provisions	22	**605**	671
		57,748	42,793
Non-current liabilities			
Loans and borrowings	19	**22,991**	32,086
Lease liabilities	19	**19,246**	19,278
Other payables	20	**6,616**	2,607
Deferred income	3	**10,315**	12,519
Provisions	22	**908**	3,176
		60,076	69,666
Total liabilities		**117,824**	112,459
Net assets		**144,820**	269,688
Equity			
Share capital	23	**16,409**	16,243
Share premium	23	**486,405**	486,382
Translation reserve	23	**18,451**	1,389
Share-based payment reserve	23	**100,126**	88,309
Fair value reserve	23	**(237)**	(171)
Retained earnings		**(476,334)**	(322,464)
Total Equity		**144,820**	269,688

These financial statements were approved by the board of directors on 27 April 2023 and were signed on its behalf by:

Hubert Gaspar, Director
27 April 2023

Company registered number: 11494381

Consolidated Statement of Changes in Equity

for the year ended 31 December 2022

	Share capital $000	Share premium $000	Translation reserve $000	Share-based payment reserve $000	Fair value reserve $000	Retained earnings $000	Total Equity $000
Balance at 1 January 2022	**16,243**	**486,382**	**1,389**	**88,309**	**(171)**	**(322,464)**	**269,688**
Total comprehensive loss for the year							
Loss for the year	**–**	**–**	**–**	**–**	**–**	**(153,870)**	**(153,870)**
Other comprehensive income	**–**	**–**	**17,062**	**–**	**(66)**	**–**	**16,996**
Total comprehensive loss for the year	**–**	**–**	**17,062**	**–**	**(66)**	**(153,870)**	**(136,874)**
Transactions with owners, recorded directly in equity							
Issue of shares under employee equity plans	**166**	**24**	**–**	**–**	**–**	**–**	**190**
Issue of shares under consulting agreements	**–**	**(1)**	**–**	**–**	**–**	**–**	**(1)**
Share-based compensation expense	**–**	**–**	**–**	**11,418**	**–**	**–**	**11,418**
Deferred tax on share-based compensation	**–**	**–**	**–**	**399**	**–**	**–**	**399**
Total transactions with owners	**166**	**23**	**–**	**11,817**	**–**	**–**	**12,006**
Balance at 31 December 2022	**16,409**	**486,405**	**18,451**	**100,126**	**(237)**	**(476,334)**	**144,820**

Consolidated Statement of Changes in Equity

for the year ended 31 December 2021

	Share capital $000	Share premium $000	Translation reserve $000	Share-based payment reserve $000	Fair value reserve $000	Retained earnings $000	Total Equity $000
Balance at 1 January 2021	12,497	339,435	292	82,714	80	(124,189)	310,829
Total comprehensive loss for the year							
Loss for the year	–	–	–	–	–	(198,275)	(198,275)
Other comprehensive income	–	–	1,097	–	(251)	–	846
Total comprehensive loss for the year	–	–	1,097	–	(251)	(198,275)	(197,429)
Transactions with owners, recorded directly in equity							
Issue of shares under employee equity plans	263	2,650	–	–	–	–	2,913
Issue of shares under collaboration agreements	170	3,965	–	–	–	–	4,135
Issue of shares under consulting agreements	3	(3)	–	–	–	–	–
Issue of shares from private placement	3,310	146,690	–	–	–	–	150,000
Share issue costs	–	(6,355)	–	–	–	–	(6,355)
Share-based compensation expense	–	–	–	19,900	–	–	19,900
Deferred tax on share-based compensation	–	–	–	(14,305)	–	–	(14,305)
Total transactions with owners	3,746	146,947	–	5,595	–	–	156,288
Balance at 31 December 2021	16,243	486,382	1,389	88,309	(171)	(322,464)	269,688

Consolidated Cash Flow Statement

for the year ended 31 December 2022

	Note	2022 $000	2021 $000
Cash flows from operating activities			
Loss for the year		**(153,870)**	(198,275)
Adjustments for:			
Depreciation and amortisation	5	**15,989**	24,364
Impairment loss on intangible assets	5	**–**	40,358
Share-based compensation	8	**11,418**	19,900
Amortization of (discount)/premium on short-term investments		**(305)**	1,514
Net finance expense	9	**2,759**	4,330
Taxation	10	**(8,058)**	(11,336)
Unrealised foreign currency gains/losses and other non-cash adjustments		**23,208**	9,687
Changes in working capital:			
Increase in inventories		**(1,384)**	(1,351)
Decrease/(increase) in trade and other receivables		**(1,131)**	(2,627)
Decrease/(increase) in research and development tax credit receivable		**779**	(1,620)
Increase/(decrease) in trade and other payables		**12,837**	(10,420)
(Decrease)/increase in deferred income		**(272)**	13,122
Increase in other non-current liabilities		**2,154**	34
Decrease in provisions		**(2,337)**	(792)
Cash used in operating activities, before tax		**(98,213)**	(113,112)
Tax paid, net of research and development tax credit received		**28,629**	(1,651)
Net cash outflow used in operating activities		**(69,584)**	(114,763)
Cash flows from investing activities			
Interest received on Short-term investments		**2,580**	412
Proceeds from the sale of other investments		**201,389**	234,732
Receipt of funds from construction deposit		**7,966**	216
Acquisition of property and equipment		**(6,514)**	(2,348)
Acquisition of intangible assets		**–**	(887)
Acquisition of other investments		**(112,281)**	(263,878)
Lease payments received on finance leases		**1,143**	181
Net cash from investing activities		**94,283**	(31,572)
Cash flows from financing activities			
Proceeds from loans and borrowings	19	**–**	7,375
Proceeds from issue of shares under employee equity plans		**212**	3,303
Proceeds from issue of shares under collaboration agreements		**–**	4,135
Proceeds from issue of shares from private placement		**–**	150,000
Costs related to issue of shares		**(119)**	(6,747)
Interest paid		**(4,908)**	(5,405)
Repayment of borrowings	19	**(786)**	–
Payment of lease liabilities	19	**(5,218)**	(5,523)
Net cash (used in)/from financing activities		**(10,819)**	147,138
Net increase in cash and cash equivalents		**13,880**	803
Cash and cash equivalents at 1 January		**60,178**	59,401
Effect of exchange rate fluctuations on cash held		**(1,419)**	(26)
Cash, cash equivalents and restricted cash at 31 December	18	**72,639**	60,178
Cash and cash equivalents		**68,424**	55,912
Restricted cash	17	**4,215**	4,266
Cash, cash equivalents and restricted cash at 31 December	18	**72,639**	60,178

1 ACCOUNTING POLICIES

1.1 NATURE OF BUSINESS AND BASIS OF PREPARATION

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 and its subsidiary undertakings are referred to in this report as the "Group". 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 has a portfolio that includes a commercial-stage product and research and development-stage product candidates.

The Company is a public limited company incorporated pursuant to the laws of England and Wales.

The Company is domiciled and registered in the UK. The registered number is 11494381 and the registered address is 245 Hammersmith Road, 3rd Floor, London, England, W6 8PW, United Kingdom.

The Company has American Depositary Shares ("ADSs") registered with the U.S. Securities and Exchange Commission (the "SEC"). The ADSs were listed on the Nasdaq Global Select Market on 31 October 2018 and were transferred to the Nasdaq Capital Market on 13 September 2022. As at 31 December 2022 each holder of ordinary shares and ADSs is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. The Company did not declare any dividends in 2022 or 2021. Following the ratio change on 10 March 2023 (see note 28) each ADS represents 10 ordinary shares of the Company.

On 9 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 4 February 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 4 February 2021. At 31 December 2021, all outstanding non-voting shares have been converted to voting ordinary shares.

The group financial statements consolidate those of the Company and its subsidiaries (together referred to as the "Group"). The parent company financial statements present information about the Company as a separate entity and not about its group.

The Group financial statements have been prepared and approved by the directors in accordance with international accounting standards in accordance with UK-adopted international accounting standards ("UK-adopted IFRS"). The Company has elected to prepare its parent company financial statements in accordance with FRS 101.

The accounting policies set out below have, unless otherwise stated, been applied consistently to all periods presented in these group financial statements and in preparing an opening IFRS Consolidated statement of financial position at 1 January 2021 for the purposes of the transition from accounting principles generally accepted in the United States of America ("US GAAP") to UK-adopted IFRSs. The consolidated financial statements were historically prepared in accordance with US GAAP, as permitted by Statutory Instrument 2015 No. 1675, "The Accounting Standards (Prescribed Bodies) (United States of America and Japan) Regulations 2015". This Statutory Instrument permitted the use of US GAAP for the consolidated financial statements for the first four years following Orchard Therapeutics plc's incorporation in 2018 through to the year ended 31 December 2021, and the Group has transitioned to IFRS for the year ended 31 December 2022.

1 ACCOUNTING POLICIES *continued*

Judgements made by the directors, in the application of these accounting policies that have a significant effect on the financial statements and estimates with a significant risk of material adjustment in the next year are set out in note 2.

1.2 TRANSITION TO UK-ADOPTED IFRSs

The Group is preparing its financial statements in accordance with UK-adopted IFRS for the first time and consequently has applied IFRS 1. An explanation of how the transition from US GAAP to UK-adopted IFRSs has affected the reported financial position, financial performance and cash flows of the Group is provided in note 29.

IFRS 1 grants certain exemptions from the full requirements of UK-adopted IFRSs in the transition period. The following exemptions have been taken in these financial statements:

– Leases - the right-of-use asset is measured at an amount equal to the lease liability on the date of transition.

– Financial instruments – classification of financial instruments is based on facts and circumstances which existed at the date of transition.

1.3 BASIS OF PREPARATION

The financial statements are prepared on the historical cost basis modified by the revaluation of certain items, as stated in the accounting policies and on a going concern basis.

The accompanying consolidated financial statements have been prepared in accordance with UK-adopted IFRS and with the requirements of the Companies Act 2006 as applicable to companies reporting under those standards. These financial statements include the accounts of the Company and its wholly owned subsidiaries, after elimination of all intercompany accounts and transactions.

Items included in the financial statements of each of the group's entities are measured using the currency of the primary economic environment in which the entity operates ('the functional currency'). The consolidated financial statements are presented in US Dollars (USD), which is Orchard Therapeutics plc's functional and presentation currency.

Amounts reported are based in thousands, except percentages, per share amounts or as otherwise noted.

1.4 GOING CONCERN

The accompanying consolidated financial statements have been prepared on a going concern basis.

The Group expects that its cash, cash equivalents, and short-term investments as of 31 December 2022, of $143.8 million, together with expected proceeds from sales of Libmeldy and the $34 million received in March 2023 from the 2023 Private Placement (see note 28), will be sufficient to fund its operations and capital expenditure requirements for at least twelve months from the date of signing of this Annual Report and Financial Statements. Management have prepared a budget to support the going concern assumption of the Group which shows the Group has sufficient resources to continue as a going concern into 2025.

1 ACCOUNTING POLICIES *continued*

1.5 BASIS OF CONSOLIDATION

Subsidiaries

Subsidiaries are entities controlled by the Group. The Group controls an entity when it is exposed to, or has rights to, variable returns from its involvement with the entity and has the ability to affect those returns through its power over the entity. In assessing control, the Group takes into consideration potential voting rights. The acquisition date is the date on which control is transferred to the acquirer. The financial statements of subsidiaries are included in the consolidated financial statements from the date that control commences until the date that control ceases.

Transactions eliminated on consolidation

Intra-group balances and transactions, and any unrealised income and expenses arising from intra-group transactions, are eliminated.

1.6 FOREIGN CURRENCY

Transactions in foreign currencies are translated to the respective functional currencies of Group entities at the foreign exchange rate ruling at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the Consolidated statement of financial position date are retranslated to the functional currency at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognised in the Consolidated statement of profit or loss. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction. Non-monetary assets and liabilities denominated in foreign currencies that are stated at fair value are retranslated to the functional currency at foreign exchange rates ruling at the dates the fair value was determined.

The Group includes realised and unrealised foreign currency transaction losses in the Consolidated statement of profit and loss.

The assets and liabilities of foreign operations are translated to the Group's presentational currency, US dollars, at foreign exchange rates ruling at the Consolidated statement of financial position date. The revenues and expenses of foreign operations are translated at an average rate for the year where this rate approximates to the foreign exchange rates ruling at the dates of the transactions.

Exchange differences arising from this translation of foreign operations are reported as an item of other comprehensive income and accumulated in the translation reserve.

1.7 FINANCIAL INSTRUMENTS

The Group financial instruments include trade and other receivables, trade and other payables, lease liabilities, cash and cash equivalents, deposits, loans and borrowings and short-term investments.

Cash and cash equivalents

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

Restricted cash and construction deposits

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on the Consolidated statement of financial position, classified within other receivables. The Group 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 statement of cash flows.

1 ACCOUNTING POLICIES *continued*

1.7 FINANCIAL INSTRUMENTS *continued*

Trade and other receivables

Trade receivables arise from product revenue and amounts due from the Group's collaboration partners and have payment terms that generally require payment within 30 to 90 days. For some Libmeldy customers, our payment terms can range from 30 days to under one year. The amount from product revenue represents amounts due from distributors in Europe, which are recognised initially at fair value, net of reserves for trade discounts and allowances, and other incentives to the extent such amounts are payable to the customer by the Group.

The Group holds the trade receivables with the objective to collect the contractual cash flows and therefore measures them subsequently at amortised cost using the effective interest rate method, less any impairment losses.

The Group monitors economic conditions to identify facts or circumstances that may indicate that its receivables are at risk of collection. The Group will provide against trade receivables for any expected credit loss that may result from a customer's inability to pay based on the composition of its accounts receivable, current economic conditions, and historical credit loss activity. Any impairment loss is recognised directly in the Consolidated statement of profit or loss.

Trade and other payables

Trade and other payables are recognised initially at fair value. Subsequent to initial recognition they are measured at amortised cost using the effective interest rate method.

Short-term investments

Short-term investments consist of debt securities with original maturities of greater than ninety days. The Group has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such debt securities represent the investment of cash that is available for current operations.

Short-term investments in debt securities have been classified as measured at fair value through other comprehensive income (FVOCI) as a) they are held within a business model whose objective is achieved by both collecting contractual cash flows and selling financial assets; and b) their contractual terms give rise on specified dates to cash flows that are solely payments of principal and interest on the principal amount outstanding.

Short-term investments in debt securities are subsequently measured at fair value. Interest income calculated using the effective interest method, foreign exchange gains and losses and impairment are recognised in profit or loss. Other net gains and losses are recognised in other comprehensive income (OCI). On derecognition, gains and losses accumulated in OCI are reclassified to profit or loss.

Borrowings

Interest-bearing borrowings are initially measured at fair value (with direct transaction costs being amortised over the life of the loan) and are subsequently measured at amortised cost using the effective interest rate method at each reporting date.

Lease liabilities

Lease liabilities are initially measured at fair value and are subsequently measured at amortised cost using the effective interest rate method at each reporting date.

1 ACCOUNTING POLICIES *continued*

1.7 FINANCIAL INSTRUMENTS *continued*

Lease receivables

Lease receivables are initially recognised at an amount equal to the Group's net investment in the lease, which comprises of the present value of lease payments and initial direct costs. Lease receivables are subsequently measured at amortised cost using the effective interest rate method, less any impairment losses.

1.8 PROPERTY, PLANT AND EQUIPMENT

Property, plant and equipment are stated at cost less accumulated depreciation and accumulated impairment losses.

Where parts of an item of property, plant and equipment have different useful lives, they are accounted for as separate items of property and equipment.

Depreciation is charged to the Consolidated statement of profit or loss on a straight-line basis over the estimated useful lives of each part of an item of property, plant and equipment. The estimated useful lives are as follows:

Lab equipment	5-10 years
Leasehold improvements	Shorter of lease term or estimated useful life
Furniture and fixtures	4 years
Computer equipment	3-5 years

Depreciation methods, useful lives and residual values are reviewed at each statement of financial position date.

Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property, plant 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 statement of profit and loss and other comprehensive loss.

1.9 INTANGIBLE ASSETS

Research and development costs

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.

Expenditure on research activities is recognised in the Consolidated statement of profit or loss as an expense as incurred.

Internal development expenditure is capitalised only if it meets the recognition criteria of IAS 38 *Intangible Assets*. Where regulatory and other uncertainties are such that the criteria are not met, the expenditure is charged to profit and loss. Where the recognition criteria are met, development costs are capitalised and amortised on a straight-line basis over their useful economic lives from product launch.

1 ACCOUNTING POLICIES *continued*

1.9 INTANGIBLE ASSETS *continued*

Other Intangibles

Other intangible assets comprise capitalised upfront payments and milestone payments to acquire license intangibles from external parties in relation to both products in development and approved products. Other intangible assets are amortised on a straight-line basis over their estimated useful economic life.

The Group makes payments to third parties for in process research and development projects. Payments generally take the form of upfront payments and milestone payments. Such payments are expensed if they represent consideration for sub-contracted future research and development services. Payments are capitalised if they represent consideration for the transfer of identifiable intellectual property developed at the risk of the third party. Any upfront or milestone payments for research activities where there is no associated identifiable intellectual property are expensed. Milestone payments related to identifiable intellectual property are capitalised when they fall due.

Intangible assets are amortised over their estimated economic lives from product launch and periodically reviewed for impairment.

Amortisation

Amortisation is charged to the Consolidated statement of profit or loss on a straight-line basis over the estimated useful lives of intangible assets. The estimated useful lives are as follows:

License intangibles	10 years

1.10 INVENTORIES

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 Group's consolidated statement of profit or loss.

Inventories are stated at the lower of cost and estimated selling price less costs to complete and sell. Inventories are recognised as an expense in the period in which the related revenue is recognised.

Cost is determined on the first-in, first-out (FIFO) method. Cost includes the purchase price, including taxes and duties and transport and handling directly attributable to bringing the inventory to its present location and condition. The cost of finished products and work in progress includes design costs, raw materials, direct labour and other direct costs and related production overheads (based on normal operating capacity).

At the end of each reporting period inventories are assessed for impairment. If an item of inventory is impaired, the identified inventory is reduced to its selling price less costs to complete and sell and an impairment charge is recognised in the profit and loss account. Where a reversal of the impairment is recognised the impairment charge is reversed, up to the original impairment loss, and is recognised as a credit in the Consolidated statement of profit and loss.

1.11 PROVISIONS

A provision is recognised in the Consolidated statement of financial position when the Group has a present legal or constructive obligation as a result of a past event, that can be reliably measured and it is probable that an outflow of economic benefits will be required to settle the obligation. Provisions are determined by discounting the expected future cash flows at a pre-tax rate that reflects risks specific to the liability.

1 ACCOUNTING POLICIES *continued*

1.12 EMPLOYEE BENEFITS

Defined contribution plans

A defined contribution plan is a post-employment benefit plan under which the Group pays fixed contributions into a separate entity and will have no legal or constructive obligation to pay further amounts. Obligations for contributions to defined contribution pension plans are recognised as an expense in the Consolidated statement of profit or loss in the periods during which services are rendered by employees.

Short-term benefits

Short-term employee benefit obligations are measured on an undiscounted basis and are expensed as the related service is provided. A liability is recognised for the amount expected to be paid under short-term cash bonus or profit-sharing plans if the Group has a present legal or constructive obligation to pay this amount as a result of past service provided by the employee and the obligation can be estimated reliably.

Share-based payment transactions

Share-based payment arrangements in which the Group receives goods or services as consideration for its own equity instruments have been classified as equity-settled share-based payment transactions.

The Group 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 recognises compensation expense for those awards over the requisite service period, which is the vesting period of the respective award. A corresponding increase in the share-based payment reserve in equity is made. The expense is recognised accordance with IFRS2 so that awards with graded vesting are treated as separate grants and the expense associated with each of these separate grants is recognised over the associated vesting period. The expense is included in the Consolidated statement of profit or loss and allocated to either research and development expenses of selling, general and administrative expenses depending on the cost centre of the employee to which the award relates.

The fair value of the awards granted is measured using the Black Scholes model, which utilizes a number of inputs to estimate the fair value of share options such as the current share price, expected term, volatility, interest rate, dividend rate and exercise price. Until the completion of the parent company's initial public offering in November 2018, the parent company had been a private company and lacked company-specific historical and implied volatility information for its shares. Therefore the expected share price volatility was estimated based on both the historical volatility of publicly traded peer companies and the Group's own volatility history. This approach is expected to continue until adequate historical data regarding the volatility of the Group's own traded share price is held.

The amount recognised as an expense is adjusted to reflect the actual number of awards for which the related service and non-market vesting conditions are expected to be met, such that the amount ultimately recognised as an expense is based on the number of awards that do meet the related service and non-market performance conditions at the vesting date.

The Group has also granted Performance-based share awards (PSUs) which vest on achievement of specific milestones, known as a non-market performance condition. Expense associated with these awards is recognised from the point in time that vesting of the award is considered probable.

1 ACCOUNTING POLICIES *continued*

1.13 REVENUE

Revenue comprises product sales and collaboration revenue. Product sales are revenues arising from contracts with customers. Collaboration revenue arises from other contracts, however, the recognition and measurement principles of IFRS 15 'Revenue from Contracts with Customers' are applied as set out below.

Product sales

Strimvelis

The Group's product sales of Strimvelis are currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. The hospital will purchase and pay for the products and submit a claim to the payer. The Group's contracted sales with the hospital contain a single performance obligation and the Group recognises revenue from product sales when the Group has satisfied its performance obligation, which is upon transferring control of the products to the hospital.

The Group evaluated the variable consideration under IFRS 15 and there is currently no variable consideration included in the transaction price for the products. Costs to manufacture and deliver the product and those associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Group estimates there is limited risk of product return, including the risk of product expiration.

Libmeldy

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

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

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

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

1 ACCOUNTING POLICIES *continued*

1.13 REVENUE *continued*

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

The Group recognises product revenue, net of variable consideration related to certain allowances and accruals, when the customer takes control of the product, which is at a point in time once the patient has been infused. Product revenue is recorded at the net sales price, or transaction price. Where there is uncertainty over variable consideration, the Group includes it in the transaction price only to the extent that it is highly probable that a significant reversal of revenue will not occur ('the revenue constraint'). The Group records estimated product revenue reserves, which are classified as a reduction in product revenue, to account for the components of variable consideration. Variable consideration includes the following components: government rebates, including performance-based rebates, and trade discounts and allowances which are described below.

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

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

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

1 ACCOUNTING POLICIES *continued*

1.13 REVENUE *continued*

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

Collaboration revenue

The terms of the Group'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 Group first evaluates collaboration arrangements to determine whether the arrangement (or part of the arrangement) represents a joint venture or joint arrangement in accordance with IAS 28 Investment in Associates and Joint Ventures and IFRS 11 Joint Arrangements pursuant to the contractual arrangement. The Group 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 these standards. Currently there are no collaborative arrangements that the Group believes fall within either of these standards. The Group has entered into one agreement with Pharming Group N.V. (the "Pharming Agreement", see Note 3) that is accounted for in line with IFRS 15 set out below.

Under IFRS 15, an entity recognises 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 recognised for arrangements determined to be within the scope of IFRS 15, the Group 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 Group satisfies each performance obligation. The Group 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 Group recognises 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 Group utilises 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 recognising revenue from license payments. The Group 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 Group to additional payments upon the achievement of performance-based milestones. These milestones are generally categorised into three types: development milestones, regulatory milestones, and sales-based milestones. The Group is also eligible to receive from Pharming tiered royalty payments on worldwide net sales. The Group 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 recognised. 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

1 ACCOUNTING POLICIES *continued*

1.13 REVENUE *continued*

meet this threshold. Milestones tied to regulatory approval, and therefore not within the Group'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 Group re-evaluates the probability of a significant reversal of the cumulative revenue recognised 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 Group may enter into an agreement that includes sales-based milestone payments and royalties in exchange for a license of intellectual property. The Group 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 commercialise a product using the licensed intellectual property.

The Group also considers whether the license is the only, or predominant, item to which the milestone payments and royalties relate. If the Group concludes the license is the predominant item in the agreement, therefore the primary driver of value, the Group 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 Group has not recognised any royalty revenue resulting from the Pharming Agreement.

IFRS 15 requires the Group 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 IFRS 15 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 Group has sold the same performance obligation separately are not available, the Group 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.

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

The Group recognises 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 Group's collaborations with Pharming, revenue attributable to research services is recognised as those services are provided, based on the costs incurred to date.

1.14 EXPENSES

Research contract costs and accruals

The Group has entered into various research and development contracts. These agreements are cancellable, and related costs are recorded as research and development expenses as incurred. When

1 ACCOUNTING POLICIES *continued*

1.14 EXPENSES *continued*

billing terms under these contracts do not coincide with the timing of when the work is performed, the Group 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 Group'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 Group. The historical accrual estimates made by the Group have not been materially different from the actual costs.

Finance income and expenses

Finance expenses include interest payable and finance charges on lease liabilities recognised in the Consolidated statement of profit or loss using the effective interest method, and the unwinding of the discount on provisions. Finance income comprises interest receivable on funds invested and interest income on lease receivables. Interest income and interest payable is recognised in profit or loss as it accrues, using the effective interest method.

1.15 TAXATION

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

Tax on the profit or loss for the year comprises current and deferred tax. Tax is recognised in the Consolidated statement of profit or loss except to the extent that it relates to items recognised directly in equity, in which case it is recognised in equity.

Current tax is the expected tax payable or receivable on the taxable income or loss for the year, using tax rates enacted or substantively enacted at the statement of financial position date, and any adjustment to tax payable in respect of previous years.

Deferred tax is provided on temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for taxation purposes. The following temporary differences are not provided for: the initial recognition of goodwill; the initial recognition of assets or liabilities that affect neither accounting nor taxable profit other than in a business combination, and differences relating to investments in subsidiaries to the extent that they will probably not reverse in the foreseeable future. The amount of deferred tax provided is based on the expected manner of realisation or settlement of the carrying amount of assets and liabilities, using tax rates enacted or substantively enacted at the statement of financial position date.

A deferred tax asset is recognised only to the extent that it is probable that future taxable profits will be available against which the temporary difference can be utilised.

United Kingdom Research and development income tax credits

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

1 ACCOUNTING POLICIES *continued*

1.15 TAXATION *continued*

employment costs for research staff, consumables, and certain internal overhead costs incurred as part of research projects for which the Group does not receive income.

The RDEC and SME credits are not dependent on the Group generating future taxable income or on the ongoing tax status or tax position of the Group. Each reporting period, the Group assesses its research and development activities and expenditures to determine whether the nature of these costs will qualify for credit under the tax relief programs and whether the claims will ultimately be realized based on the allowable reimbursable expense criteria established by the UK government. The Group expects a proportion of expenditures incurred in relation to its pipeline research, clinical trials management, and manufacturing development activities to be eligible for the research and development tax relief programs for the year ended 31 December 2022. The Group has qualified under the more favourable SME regime for the year ended 31 December 2021 and expects to qualify under the SME regime for the year ended 31 December 2022.

The Group recognises 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. The SME program credits as a tax benefit and RDEC program credits as an offset against research and development expenses in the Consolidated statement of profit or loss.

1.16 LEASES

At the inception of a contract, the Group assesses whether a contract is, or contains, a lease. A contract is, or contains, a lease if the contract conveys the right to control the use of an identified asset for a period of time in exchange for consideration.

Leases as a lessee

Right of use 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. Lease liabilities with a term greater than one year and their corresponding right-of-use assets are recognised on the Consolidated statement of financial position at the commencement date of the lease based on the present value of lease payments over the expected lease term.

The Group recognises a right-of-use asset and a lease liability at the lease commencement date. The right-of-use asset is initially measured at cost, which comprises the initial amount of the lease liability adjusted for any lease payments made at or before the commencement date, plus any initial direct costs incurred, less any lease incentives received.

The Group 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 Group has not identified any material short-term leases, either individually or in the aggregate.

As the Group's leases do not provide an implicit rate, the Group utilised the appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralised basis over a similar term as the lease an amount equal to the lease payments in a similar economic environment. The Group estimated the incremental borrowing rate based on the Group'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 Group allocates the consideration in the contract to each lease component on the basis of its relative stand-alone price and the aggregate stand-alone price of the non-lease components in accordance with the principles of IFRS 16. The Group calculated the stand-alone prices of the lease and non-lease components using financial information readily available as part of its master services arrangement and other representative data.

1 ACCOUNTING POLICIES *continued*

1.16 LEASES *continued*

The right-of-use asset is subsequently depreciated using the straight-line method from the commencement date to the earlier of the end of the lease term or the end of the useful life of the right-of-use asset. In addition, the right-of-use asset is periodically reduced by impairment losses, if any, and adjusted for certain remeasurements of the lease liability.

The lease liability is initially measured at the present value of the lease payments that are not paid at the commencement date, discounted using the interest rate implicit in the lease or, if that rate cannot be readily determined, the Group's incremental borrowing rate.

Lease payments included in the measurement of the lease liability comprise the following:

– fixed payments, including in-substance fixed payments

– variable lease payments that depend on an index or a rate, initially measured using the index or rate as at the commencement date

– lease payments in an optional renewal period if the Group is reasonably certain to exercise an extension option, and

– penalties for early termination of a lease unless the Group is reasonably certain not to terminate early.

The lease liability is measured at amortised cost using the effective interest method. It is remeasured when there is a change in future lease payments arising from a change in an index or rate, there is a change in the Group's estimate of the amount expected to be payable under a residual value guarantee, if the Group changes its assessment of whether it will exercise a purchase, extension or termination option or if there is a revised in-substance fixed lease payment.

When the lease liability is remeasured in this way, a corresponding adjustment is made to the carrying amount of the right-of-use asset, to the extent that the right-of-use asset is reduced to nil, with any further adjustment required from the remeasurement being recorded in profit or loss.

Leases as a lessor

When the Group acts as a lessor, it determines at lease inception whether each lease is a finance lease or an operating lease.

To classify each lease, the Group makes an overall assessment of whether the lease transfers substantially all of the risks and rewards incidental to ownership of the underlying asset. If this is the case, then the lease is a finance lease; if not, then it is an operating lease. As part of this assessment, the Group considers certain indicators such as whether the lease is for the major part of the economic life of the asset.

When the Group is an intermediate lessor, it accounts for its interests in the head lease and the sub-lease separately. It assesses the lease classification of a sub-lease with reference to the right-of-use asset arising from the head lease, not with reference to the underlying asset.

1 ACCOUNTING POLICIES *continued*

1.17 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 the purpose of this calculation, outstanding options and unvested restricted shares are considered potential dilutive ordinary shares. Since the Group 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.

Share option and unvested shares from share plans and consulting agreements 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.

1.18 EQUITY

Share Capital and Share Premium

Ordinary shares are classified as equity. The nominal value of the shares is recorded in share capital. Any excess proceeds received for the issuance of ordinary shares over the nominal value is recorded in share premium.

Incremental costs directly attributable to the issue of new shares or options are shown in share premium in equity as a deduction, net of tax, from the proceeds.

Translation Reserve

The translation reserve comprises all foreign exchange differences arising from the translation of the financial statements of foreign operations.

1.19 UK-ADOPTED IFRS NOT YET ADOPTED

The following UK-adopted IFRSs have been issued but have not been adopted by the Group in these consolidated financial statements. Their adoption is not expected to have a material effect on the financial statements unless otherwise indicated:

- IFRS 17 *Insurance Contracts*
- Amendments to IAS 8 *Accounting Policies, Changes in Accounting Estimates and Errors:* Definition of accounting estimates
- Amendments to IAS 1 *Presentation of Financial Statements* and IFRS Practice Statement 2 *Making Materiality Judgements: Disclosure of Accounting Policies*
- Amendments to IAS 1 *Presentation of Financial Statements*: Classification of Liabilities as Current or Non-current
- Amendments to IAS 12 *Income Taxes*: Deferred Tax Related to Assets and Liabilities Arising from a Single Transaction
- Initial Application of IFRS 17 and IFRS 9 – Comparative Information (Amendments to IFRS 17)
- Amendments to IFRS 10 and IAS 28: Sale or Contribution of Assets between an Investor and its Associate or Joint Venture

2 ACCOUNTING ESTIMATES AND JUDGEMENTS

In preparing the financial statements, management had made judgements and estimates that affect the application of the Group's accounting policies and the reported amounts of assets and liabilities, income and expenses. Management have not identified any estimates or judgements which they believe are significant and may present a significant risk of material adjustment in the next financial period.

Estimates and underlying assumptions are reviewed on an ongoing basis. Revisions to estimates are recognised prospectively.

Our significant accounting policies are described in greater detail in Note 1 to our consolidated financial statements in this Annual Report.

Whilst there are no significant estimates identified, other areas of estimation uncertainty have been identified as follows:

A) EXPENSES, ACCRUALS AND PREPAYMENTS FOR CLINICAL RESEARCH ARRANGEMENTS

The Group has entered into various research and development contracts with clinical research organisations (CROs), clinical manufacturing organisations (CMOs), research institutions and other vendors. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. When billing terms under these contracts do not coincide with the timing of when the work is performed, management is first required to make estimates of the expense to be recognised in respect of the contracts such that the expense reflects the pattern of work performed. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service.

Subsequently, management is required to calculate the associated accrual or prepayment balance for each contract, based on the difference between the cumulative amount expensed under the contract to date and the cumulative amount invoiced to date. Given the difficulty in estimating the stage of completion of a clinical trial, or with obtaining the required information from the CRO/CMO, this is considered an area of estimation uncertainty.

B) IMPAIRMENT OF INTANGIBLE ASSETS

Annually, the Group considers whether intangible assets are impaired. Where an indication of impairment is identified the estimation of recoverable value requires estimation of the recoverable value of the asset. This requires estimation of the value in use of the asset.

The recoverable amounts of the intangible assets are a source of estimation uncertainty and determining this involved the use of assumptions around the potential cash flows from the assets.

2 ACCOUNTING ESTIMATES AND JUDGEMENTS *continued*

C) VALUATION OF SHARE-BASED COMPENSATION

We measure share-based awards granted to employees, non-employees and directors based on the fair value on the date of the grant and recognise compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. Forfeitures are accounted for as they occur. Generally, we issue share-based awards in the form of stock options with only service-based vesting conditions. We have also issued share-based awards with performance-based vesting conditions for which the expense is recognised when achievement of such performance conditions becomes probable.

The fair value of each share option is estimated on the date of grant using the Black-Scholes option pricing model. Until the completion of our initial public offering in November 2018, we had been a private company and lacked company-specific historical and implied volatility information for our shares. Therefore, we estimate our expected share price volatility based on the historical volatility of publicly traded peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded share price. The expected term of our share options has been determined utilising the "simplified method" for awards that qualify as "plain-vanilla" options.

The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends on our ordinary shares and do not expect to pay any cash dividends in the foreseeable future.

D) RESEARCH AND DEVELOPMENT TAX CREDIT

Each reporting period, management evaluates which tax relief programs the Group is expected to be eligible for and calculates a tax credit based on the amount of relevant expenditure 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 realised. Based on criteria established by HM Revenue and Customs ("HMRC"), management of the Group expects a proportion of expenditures being carried in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for the research and development tax relief programs

The Group 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 realised based on the allowable reimbursable expense criteria established by the U.K. government which are subject to interpretation. At each period end, the Group estimates the reimbursement available to the Group based on available information at the time. The Group is required to estimate the percentage of staff time allocated to each project as well as the percentage of some allowable costs.

The Group recognises tax 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.

3 REVENUE FROM CONTRACTS WITH CUSTOMERS

	2022 $000	2021 $000
Product sales	**20,610**	700
Collaboration revenue	**2,045**	975
Total	**22,655**	**1,675**

(I) PRODUCT REVENUE

In the following table, revenue is disaggregated by product and primary geographical market.

	2022 $000	2021 $000
Libmeldy	**18,796**	–
Strimvelis	**1,814**	700
Total product revenue	**20,610**	**700**
Primary geographical markets		
Libmeldy		
United Kingdom	**6,322**	**–**
Italy	**5,544**	**–**
France	**3,883**	**–**
Germany	**3,047**	**–**
	18,796	
Strimvelis		
Italy	**1,814**	**700**
Total product revenue	**20,610**	**700**

As at 31 December 2022, the Group recognises in its consolidated statement of financial position the following revenue deduction and reserves associated with Libmeldy contracts:

	2022 $000	2021 $000
Variable consideration and other deductions from revenue in the period recognised as a credit against trade receivables.	**4,390**	–
Government rebate recognised as an other current liability	**2,300**	–
	6,690	**–**

(II) COLLABORATION REVENUE

On 1 July 2021, the Group 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 Group 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 Group and Pharming will explore the application of non-toxic conditioning regimen for use with OTL-105 administration.

3 REVENUE FROM CONTRACTS WITH CUSTOMERS *continued*

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

The Group also entered into a Share Purchase Agreement with Pharming on 1 July 2021 (the "SPA"), pursuant to which the Group 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 Group'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 Group's ordinary shares as part of the SPA, and the license and collaboration agreement, which conveys the license and provides for the Group 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 Group considers them a single arrangement for accounting purposes. The total upfront payments of $17.5 million are comprised of $4.1 million attributed to the equity sold to Pharming and $13.4 million attributed to the Collaboration Agreement.

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

The Group 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 Group. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred consistent with the cost-to-cost method. The estimated costs associated with the remaining efforts required to complete the performance obligations may change which may impact revenue recognition and the Group regularly evaluates and, when necessary, updates the costs associated with the remaining efforts. Accordingly, revenue may fluctuate from period to period due to revisions to estimated costs resulting in a change in the measure of progress for the performance obligation or if the transaction price changes due to inclusion of any milestone payments that become unconstrained.

3 REVENUE FROM CONTRACTS WITH CUSTOMERS *continued*

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

	2022 $000	2021 $000
Reimbursement revenue	**1,776**	843
Upfront and milestone payment revenue	**269**	132
	2,045	**975**

The Group had $0.5 million due from Pharming included in trade receivables as of 31 December 2022 (2021: $0.8 million).

As of 31 December 2022, the Group had contract liabilities of $11.3 million, of which $1.0 million was classified as current and $10.3 million was classified as long-term in the consolidated statement of financial position. The deferred income balance represents the portion of the upfront payments received related to the performance obligation that remains partially unsatisfied as of 31 December 2022. The upfront and milestone payment revenue recognised in each year was previously included in the deferred income balance at the previous reporting date.

4 SEGMENT INFORMATION

The Group 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 Group's operations are reported on a consolidated basis for purposes of segment reporting.

All material long-lived assets of the Group reside in the United States or United Kingdom. The Group had property and equipment, net, of $7.5 million and $0.6 million located in the United Kingdom and United States, respectively, as of 31 December 2022. The Group had property and equipment, net, of $3.6 million and $1.2 million located in the United Kingdom and United States, respectively, as of 31 December 2021. The Group had right-of-use assets in the United States and United Kingdom of $ 2.3 million and $10.5 million, respectively as of 31 December 2022. The Group had right-of-use assets in the United States and United Kingdom of $3.1 million and $10.8 million, respectively as of 31 December 2021.

5 OPERATING LOSS

	Note	2022 $000	2021 $000
The following items have been included in operating loss:			
Depreciation – Property, plant and equipment	12	**2,397**	2,152
Depreciation – Right-of-use assets	25	**4,367**	6,560
Amortisation of intangible assets	13	**9,225**	15,652
Impairment loss on intangible assets	13	**–**	40,358
Loss on sale of property, plant and equipment	12	**114**	166
Cost of inventories included in cost of sales		**2,281**	148
Net foreign exchange loss		**24,344**	1,148

6 LOSS PER SHARE

The calculation of basic and diluted loss per share has been based on the following loss attributable to ordinary shareholders and the weighted-average number of ordinary shares outstanding.

	2022	2021
Loss attributable to ordinary shareholders ($000)	**(153,870)**	(198,275)
Weighted-average number of ordinary shares	**127,975,062**	123,963,762
Basic / diluted loss per share ($)	**(1.20)**	(1.60)

Since the Group 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, 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 be anti-dilutive:

	2022	2021
Share options	**13,076,959**	14,042,781
Uninvested shares from share plan and consulting agreement	**2,253,199**	512,908
	15,330,158	**14,555,689**

7 AUDITORS' REMUNERATION

During the year the Group obtained the following services from the Company's auditors:

	2022 $000	2021 $000
Fees payable to PricewaterhouseCoopers LLP and its associates:		
Audit of the parent company and consolidated financial statements	**1,014**	986
Audit of subsidiaries pursuant to legislation	**317**	246
Audit-related assurance services	**163**	123
Other services	**5**	5
Total fees paid to PricewaterhouseCoopers LLP	**1,499**	**1,360**

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 2023 Annual General Meeting ("AGM").

8 EMPLOYEE COSTS AND NUMBERS

	2022 $000	2021 $000
Salaries and bonus	**40,095**	43,804
Social security contributions	**4,700**	3,209
Other employee benefits	**1,869**	2,419
Contributions to defined contribution plans	**1,618**	1,736
Equity-settled share-based payments	**11,418**	19,900
Termination benefits	**1,781**	–
	61,481	71,068

The average number of persons employed by the Group (including directors) during the year was as follows:

	2022	2021
UK	**138**	146
Offshore	**66**	92
	204	**238**

Transactions with key management personnel are contained within note 27.

Director's emoluments are contained within note 12 of the Parent Company financial statements.

9 FINANCE INCOME AND EXPENSE

	2022 $000	2021 $000
Finance income		
Interest income on debt securities measured at FVOCI	**1,543**	412
Interest income on lease receivable	**1,037**	1,057
	2,580	1,469
Finance expense		
Interest expense on loan and borrowings	**(3,079)**	(2,497)
Interest expense on lease liabilities	**(2,260)**	(3,302)
	(5,339)	(5,799)
Net finance expense	**(2,759)**	(4,330)

10 TAXATION

RECOGNISED IN THE CONSOLIDATED STATEMENT OF PROFIT OR LOSS

	2022 $000	2021 $000
Current tax expense/(credit)		
Current year tax credit	**(4,125)**	(10,011)
Adjustments for prior years	**(1,962)**	(2,594)
Current tax expense/(credit)	**(6,087)**	(12,605)
Deferred tax expense		
Origination and reversal of temporary differences	**(1,957)**	(200)
Adjustments for prior years	**(14)**	1,469
Deferred tax (credit)/expense	**(1,971)**	1,269
Total tax credit	**(8,058)**	(11,336)
Current tax expense/(credit)		
United Kingdom	**(7,000)**	(12,302)
Overseas	**913**	(303)
	(6,087)	(12,605)
Deferred tax (credit)/expense		
United Kingdom	**–**	–
Overseas	**(1,971)**	1,269
	(1,971)	1,269
Total tax credit	**(8,058)**	(11,336)

RECOGNISED DIRECTLY IN EQUITY

	2022 $000	2021 $000
Deferred tax on share-based payments recognised directly in equity	**399**	(14,305)

RECONCILIATION OF EFFECTIVE TAX RATE

	2022 $000	2021 $000
Loss for the year	**(153,870)**	(198,275)
Total tax credit	**8,058**	11,336
Loss excluding taxation	**(161,928)**	(209,611)
Tax using the UK corporation tax rate of 19 % (2021: 19%)	**(30,766)**	(39,826)
Effect of tax rates in foreign jurisdictions	**(69)**	116
Change in tax rate	**(8,240)**	(38,785)
Tax effect of:		
Non-deductible expenses	**1,324**	(485)
Research and development tax credit and benefit of other tax incentives	**(5,909)**	(5,519)
Employee share options	**1,626**	3,030
Unrecognised deferred tax asset	**35,465**	70,329
Others	**(1,489)**	(196)
Total tax credit	**(8,058)**	(11,336)

10 TAXATION *continued*

The Group's income tax credit for the year ended 31 December 2022, compared to the year ended 31 December 2021, decreased primarily due to a reduction in the UK Research and Development Tax Credit the Group was able to claim for the year.

During 2021, the U.K. Government announced that from 1 April 2023, the corporation tax rate would increase to 25%. This new law was substantively enacted on 24 May 2021.

11 DEFERRED TAX ASSETS AND LIABILITIES

Movement in recognised deferred tax balances during the year

					31 December 2022	
	1 January 2022 $000	Recognised in Consolidated statement of profit or loss $000	Directly in equity $000	Net $000	Deferred tax assets $000	Deferred tax liabilities $000
Tax losses	**11**	**(11)**	**–**	**–**	**–**	**–**
Research and development tax credit	**587**	**160**	**–**	**747**	**747**	**–**
Research and development capitalisation	**–**	**2,285**	**–**	**2,285**	**2,285**	**–**
Share–based payments	**1,632**	**(662)**	**399**	**1,369**	**1,369**	**–**
Accrued expenses	**784**	**171**	**–**	**955**	**955**	**–**
Fixed assets	**(26)**	**(46)**	**–**	**(72)**	**–**	**(72)**
Leases	**(232)**	**101**	**–**	**(131)**	**–**	**(131)**
Other	**357**	**(27)**	**–**	**330**	**330**	**–**
	3,113	**1,971**	**399**	**5,483**	**5,686**	**(203)**

Movement in recognised deferred tax during the prior year

					31 December 2021	
	1 January 2021 $000	Recognised in Consolidated statement of profit or loss $000	Directly in equity $000	Net $000	Deferred tax assets $000	Deferred tax liabilities $000
Tax losses	357	(346)	–	11	11	–
Research and development tax credit	–	587	–	587	587	–
Research and development capitalisation	–	–	–	–	–	–
Share–based payments	17,234	(1,297)	(14,305)	1,632	1,632	–
Accrued expenses	1,001	(217)	–	784	784	–
Fixed assets	2	(28)	–	(26)	–	(26)
Leases	(225)	(7)	–	(232)	–	(232)
Other	318	39	–	357	357	–
	18,687	(1,269)	(14,305)	3,113	3,371	(258)

11 DEFERRED TAX ASSETS AND LIABILITIES *continued*

Unrecognised deferred tax assets

For the years ended 31 December 2022 and 2021, the Group had cumulative U.K. net operating loss carry forwards of approximately $633.4 million and $506.2 million, respectively. U.K. losses not surrendered may be carried forward indefinitely, subject to numerous utilization criteria and restrictions.

For the years ended 31 December 2022 and 2021, the Group also had U.S. federal orphan drug tax credits of $0.7 million and $0.6 million, respectively, and U.S. state research and development tax credits of $2.2 million and $2.4 million. The U.S. federal orphan drug tax credits expire in 2042, while the U.S. state research and development credits may be carried forward indefinitely.

A deferred tax asset is recognised only to the extent that it is probable that future taxable profits will be available against which the temporary difference can be utilised.

In measuring the Group's deferred tax assets, the Group considers all available evidence, both positive and negative, to determine whether, based on the weight of that evidence, it is probable that future taxable profits will be available against which the temporary difference can be utilised. 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.

Management has considered the Group's history of cumulative net losses in the U.K., along with estimated future taxable income and has concluded that it is more likely than not that the Group will not realize the benefits of its U.K. deferred tax assets and U.S. state research and development tax credits. Accordingly, no deferred tax asset is recognised in respect of these.

12 PROPERTY, PLANT AND EQUIPMENT

	Leasehold improvements $000	Furniture & fixtures $000	Computer equipment $000	Lab equipment $000	Total $000
Cost					
Balance at 1 January 2021	2,521	304	1,066	5,114	9,005
Additions	51	–	1,075	1,237	2,363
Disposals	(51)	–	(43)	(237)	(331)
Foreign exchange movements	(21)	(1)	(10)	(80)	(112)
Balance at 31 December 2021	2,500	303	2,088	6,034	10,925
Balance at 1 January 2022	**2,500**	**303**	**2,088**	**6,034**	**10,925**
Additions	**4,072**		**210**	**2,128**	**6,410**
Disposals	**(1,246)**	**(71)**	**(52)**	**–**	**(1,369)**
Foreign exchange movements	**(257)**	**(6)**	**(93)**	**(681)**	**(1,037)**
Balance at 31 December 2022	**5,069**	**226**	**2,153**	**7,481**	**14,929**
Depreciation and impairment					
Balance at 1 January 2021	1,190	111	262	2,661	4,224
Charge for the year	644	72	354	1,082	2,152
Disposals	(28)	–	(25)	(95)	(148)
Foreign exchange movements	(17)	(1)	(3)	(49)	(70)
Balance at 31 December 2021	1,789	182	588	3,599	6,158
Balance at 1 January 2022	**1,789**	**182**	**588**	**3,599**	**6,158**
Charge for the year	**648**	**64**	**636**	**1,049**	**2,397**
Disposals	**(1,128)**	**(65)**	**(29)**	**–**	**(1,222)**
Foreign exchange movements	**(111)**	**(5)**	**(28)**	**(398)**	**(542)**
Balance at 31 December 2022	**1,198**	**176**	**1,167**	**4,250**	**6,791**
Net book value					
At 1 January 2021	1,331	193	804	2,453	4,781
At 31 December 2021	711	121	1,500	2,435	4,767
At 31 December 2022	**3,871**	**50**	**986**	**3,231**	**8,138**

13 INTANGIBLE ASSETS

	Licenses $000
Cost	
Balance at 1 January 2021	164,719
Additions	1,253
Effect of movements in foreign exchange	(1,912)
Balance at 31 December 2021	164,060
Balance at 1 January 2022	**164,060**
Effect of movements in foreign exchange	**(16,502)**
Balance at 31 December 2022	**147,558**
Amortisation and impairment	
Balance at 1 January 2021	44,520
Amortisation for the year	15,652
Impairment charge	40,358
Effect of movements in foreign exchange	122
Balance at 31 December 2021	100,652
Balance at 1 January 2022	**100,652**
Amortisation for the year	**9,225**
Effect of movements in foreign exchange	**(10,611)**
Balance at 31 December 2022	**99,266**
Net book value	
At 1 January 2021	120,199
At 31 December 2021 and 1 January 2022	63,408
At 31 December 2022	**48,292**

Intangible assets comprise capitalised upfront payments and milestone payments to acquire license intangibles from external parties in relation to both products in development and approved products.

IMPAIRMENT

In March 2022, the Group announced a new strategic plan and restructuring, which included reducing its investment in the future development of OTL-102 for treatment of X-CGD, OTL-103 for treatment of WAS and Strimvelis. As a result of this announcement, the Group recorded an impairment of $40.4 million in 2021 against licenses for X-CGD, X-SCID, OTL-103, WAS and Strimvelis.

No impairment losses were recognised in 2022.

continued

13 INTANGIBLE ASSETS *continued*

AMORTISATION AND IMPAIRMENT CHARGE

The amortisation and impairment charge are recognised in the following line items in the Consolidated statement of profit or loss:

	2022 $000	2021 $000
Research and development expense	**9,225**	56,010

14 SUBSIDIARY UNDERTAKINGS

The table below provides details of the Company's subsidiary undertakings as at 31 December 2022.

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

The following table outlines the country of incorporation and registered office of each of the subsidiary undertakings:

	Country of incorporation	Registered office
Orchard Therapeutics (Europe) Limited	United Kingdom	245 Hammersmith Road, 3rd Floor, London, W6 8PW 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 Untermuli 7 6300 Zug, Switzerland
Orchard Therapeutics (Sweden) AB	Sweden	c/o (Intertrust Sweden) AB, Norra Vallgatan 70, 211 22 Malmo, Sweden

All outstanding liabilities of Orchard Therapeutics (Europe) Limited as at 31 December 2022 have been provided with a parent company guarantee under s.479C of the Companies Act 2006. Their individual financial statements for the year ended 31 December 2022 are therefore entitled to exemption from audit under s.479A of the Companies Act 2006.

15 SHORT-TERM INVESTMENTS

	2022 $000	2021 $000
Current		
U.S. government securities	**1,984**	–
Corporate bonds	**25,475**	94,794
Commercial paper	**47,867**	69,401
	75,326	164,195

Investments in commercial paper have fixed coupon rates at 1.1% - 5.1% (2021: 0.1–0.3%) and mature between 1 January 2023 and 31 August 2023 (2021: 1 January 2022 and 30 November 2022). Investments in corporate bonds have fixed coupon rates at 0.4% - 5.7% (2021: 0.2–3.2%) and mature between 1 January 2023 and 31 October 2024 (2021: 1 January 2022 and 31 October 2023).

16 INVENTORIES

	2022 $000	2021 $000
Raw materials	**492**	1,719
Work in progress	**2,906**	296
	3,398	2,015

Included within inventories is $nil (2021: $nil) expected to be recovered in more than 12 months.

The Group recognised $2,281,000 (2021: $148,000) of inventories as an expense within cost of sales during the year. Inventory write-offs in the year amounted to $nil (2021: $nil). The write-down of inventories to net realisable value amounted to $nil (2021: $nil).

17 TRADE AND OTHER RECEIVABLES

	2022 $000	2021 $000
Amounts due within one year		
Trade receivables	**8,467**	1,480
Prepaid external research and development expenses	**881**	2,438
Other prepayments	**1,817**	6,128
VAT receivable	**1,077**	1,169
Construction deposit	**–**	7,909
Other receivables	**2,706**	3,311
	14,948	22,435
Amounts due in more than one year		
Deposits	**1,048**	1,404
Restricted cash	**4,215**	4,266
Other receivables	**462**	693
	5,725	6,363
	20,673	28,798

17 TRADE AND OTHER RECEIVABLES *continued*

RESTRICTED CASH

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on the Group's consolidated statement of financial position. The Group has an outstanding letter of credit for $3.0 million associated with a lease and is required to hold this amount in a standalone bank account as of 31 December 2022 (2021: $3.0 million). The Group is also contractually required to maintain a cash collateral account associated with corporate credit cards and other leases in the amount of $1.2 million as of 31 December 2022 (2021: $1.3 million).

The Group 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 statement of cash flows.

18 CASH AND CASH EQUIVALENTS

	2022 $000	2021 $000
Cash deposits held at bank	**41,263**	14,308
Money market funds	**1,239**	21,085
Government bonds	**5,200**	7,321
Corporate bonds	**6,600**	–
Commercial papers	**14,122**	13,198
Cash and cash equivalents per statement of financial position	**68,424**	55,912
Restricted cash	**4,215**	4,266
Cash and cash equivalents per cash flow statement	**72,639**	60,178

19 INTEREST-BEARING LOANS AND BORROWINGS

This note provides information about the contractual terms of the Group's interest-bearing loans and borrowings, which are measured at amortised cost. For more information about the Group's exposure to interest rate and foreign currency risk, see note 24.

	2022 $000	2021 $000
Non-current liabilities		
Term Loan	**22,991**	32,086
Lease liabilities	**19,246**	19,278
	42,237	51,364
Current liabilities		
Term Loan	**9,429**	786
Lease liabilities	**6,424**	7,335
	15,853	8,121
	58,090	59,485

19 INTEREST-BEARING LOANS AND BORROWINGS *continued*

TERMS AND REPAYMENT SCHEDULE

The terms and conditions of outstanding loans are as follows.

	Currency	Maturity date	Interest rate	Carrying amount 2022 $000	Carrying amount 2021 $000
Term loan	USD	2026	LIBOR+5.95%	**32,665**	33,203
Lease liabilities	USD	2023-30	8.6%-9.6%	**14,508**	16,264
Lease liabilities	GBP	2023-32	9.60%	**6,151**	1,021
Lease liabilities	EUR	2024	8.00%	**5,011**	9,328
				58,335	59,816
Less: unamortised debt issue costs				**(245)**	(331)
Total interest-bearing liabilities				**58,090**	59,485

During the year ended 31 December 2022, the Group recognised $3.1 million of interest expense related to the bank loan (2021: $2.5 million). The effective annual interest rate as of 31 December 2022 on the outstanding debt under the Term Loan was approximately 9.2% (2021: 8.4%).

TERM LOAN

In May 2019, the Group 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 Group 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 Group 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 Group 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 1 July 2022 and no later than 1 July 2023 upon certain regulatory approvals and evidence of the Group 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 1 July 2023 and no later than 1 July 2024 upon evidence of the Group having $100 million in cash and cash equivalent investments and attaining a pre-specified trailing 12-month revenue target.

Each term loan under the Amended Credit Facility bears interest at an annual rate equal to 5.95% plus LIBOR. The Group is required to make interest-only payments on the term loan for 18 months following the date of the Amended Credit Facility, unless the Group is eligible for the second tranche, in which case the Group 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 Group to the Lenders in consecutive monthly instalments until the loan maturity date. In addition, a final payment of 3.5% of the principal is due on the loan maturity date. The Group 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.

19 INTEREST-BEARING LOANS AND BORROWINGS *continued*

The Amended Credit Facility includes affirmative and negative covenants. The affirmative covenants include, among others, covenants requiring the Group 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 Group 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 Group is also subject to an ongoing minimum cash financial covenant in which the Group must maintain unrestricted cash in an amount not less than $20.0 million following the utilization of the second term loan and not less than $35.0 million following the utilization of the third term loan.

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

CHANGES IN LIABILITIES FROM FINANCING ACTIVITIES

	Term loan $000	Lease liabilities $000	Total $000
Balance at 1 January 2022	**32,872**	**26,613**	**59,485**
Changes from financing cash flows			
Repayment of borrowings	**(786)**	**–**	**(786)**
Payment of lease liabilities	–	**(5,218)**	**(5,218)**
Total changes from financing cash flows	**(786)**	**(5,218)**	**(6,004)**
The effect of changes in foreign exchange rates	**–**	**(820)**	**(820)**
Other changes			
New leases	**–**	**6,248**	**6,248**
Lease modification and remeasurements	**–**	**(1,153)**	**(1,153)**
Capitalised borrowing costs	**86**	**–**	**86**
Interest expense	**2,896**	**2,260**	**5,156**
Interest paid presented as financing cashflow	**(2,648)**	**(2,260)**	**(4,908)**
Total other changes	**334**	**5,095**	**5,429**
Balance at 31 December 2022	**32,420**	**25,670**	**58,090**

19 INTEREST-BEARING LOANS AND BORROWINGS *continued*

CHANGES IN LIABILITIES FROM FINANCING ACTIVITIES

	Term loan $000	Lease liabilities $000	Total $000
Balance at 1 January 2021	25,065	33,102	58,167
Changes from financing cash flows			
Proceeds from loans and borrowings	7,375	–	7,375
Repayment of borrowings	–	–	–
Payment of lease liabilities	–	(5,523)	(5,523)
Total changes from financing cash flows	7,375	(5,523)	1,852
The effect of changes in foreign exchange rates	–	(968)	(968)
Other changes			
New leases	–	535	535
Lease modifications and remeasurements	–	(533)	(533)
Capitalised borrowing costs	10	–	10
Interest expense	2,525	3,302	5,827
Interest paid presented as financing cashflow	(2,103)	(3,302)	(5,405)
Total other changes	432	2	434
Balance at 31 December 2021	32,872	26,613	59,485

20 TRADE AND OTHER PAYABLES

	2022 $000	2021 $000
Current liabilities		
Trade payables	**9,318**	10,008
Accrued external research and development expenses	**11,230**	9,273
Accrued payroll and related expenses	**12,312**	8,521
Accrued milestone payments	**85**	2,058
Accrued professional fees	**2,263**	854
Accrued other	**2,823**	2,941
Accrued government rebates	**2,300**	–
	40,331	33,655
Non-current liabilities		
Other payables	**6,616**	2,607
	6,616	2,607
	46,947	36,262

Other payables consists of Royalty payments on product sales due in more than one year and deposits received from tenants on leases where the Group is a lessor.

21 EMPLOYEE BENEFITS

DEFINED CONTRIBUTION PLANS

The Group makes contributions to private defined contribution pension plans on behalf of its employees. The Group matches its employee contributions up to six percent of each employee's annual salary based on the jurisdiction the employees are located. The Group paid $1.6 million in matching contributions for the year 31 December 2022 (2021: $1.7 million).

SHARE-BASED PAYMENTS

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

The numbers of options and restricted stock units, the weighted average grant date fair values per stock option and per share, and the weighted average exercise prices are all shown below on a per ordinary share basis. As at 31 December 2022 the parent company's ADSs that are listed on the NASDAQ Capital Market each represent one ordinary share. Following the ratio change on 10 March 2023 (see note 28) each ADS represents ten ordinary shares.

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

Measurement of fair value

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 utilising historical data. Until the completion of the parent company's initial public offering in November 2018, the parent company had been a private company and lacked company-specific historical and implied volatility information for the shares. Therefore, management estimate the expected share price volatility based on both the historical volatility of publicly traded peer companies and our own volatility history. It is expected to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded share price. The peer companies are taken from 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:

21 EMPLOYEE BENEFITS *continued*

	2022	2021
Risk-free interest rate	**1.3% - 4.2%**	0.4% - 1.5%
Expected term (in years)	**3.1 - 7.7**	5.0 - 7.0
Expected volatility	**70.8% - 80.4%**	70.4% - 76.8%
Expected dividend rate	**0.0%**	0.0%

SHARE OPTIONS

The number and weighted average exercise prices of share options are as follows:

	Shares Number	Weighted average exercise price per share $	Weighted average remaining contract life Years
Outstanding at 1 January 2022	**17,300,740**	**6.57**	
Granted during the year	**4,600,154**	**0.56**	
Exercised during the year	**(699,234)**	**–**	
Forfeited during the year	**(4,777,493)**	**6.81**	
Outstanding at 31 December 2022	**16,424,167**	**1.56**	**7.38**
Exercisable as at 31 December 2022	**9,212,552**	**2.28**	**6.26**

	Shares Number	Weighted average exercise price per share $	Weighted average remaining contract life Years
Outstanding at 1 January 2021	13,895,643	7.96	7.16
Granted during the year	8,489,856	4.75	
Exercised during the year	(1,727,254)	1.59	
Forfeited during the year	(3,357,505)	10.30	
Outstanding at 31 December 2021	17,300,740	6.57	7.82
Exercisable as at 31 December 2021	7,880,668	6.90	6.26

The options outstanding at the year-end have an exercise price in the range of nil to $15.09.

RESTRICTED SHARE UNITS

CEO Award

The Group granted 195,000 performance-based Restricted Share Units ('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 2 January 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 31 December 2023 and Dr. Gaspar remains continuously employed with the Group through to 2 January 2024. The milestones relate to the achievement of specific clinical and regulatory milestones. No performance-based share unit performance conditions associated with the CEO award were deemed probable and none vested during the year ended 31 December 2022 (2021: none).

21 EMPLOYEE BENEFITS *continued*

Time-based restricted share units

Time-based restricted share units vest in equal annual instalments over a three-year period. During the year ended 31 December 2022, the total fair value of time-based RSU's that vested was $0.3 million (2021: $0.3 million).

	Performance-based RSUs Number	Time-based RSUs Number	Total RSUs Number	Weighted average grant date fair value per share $
Outstanding at 1 January 2022	**195,000**	**123,333**	**318,333**	**6.41**
Granted during the year	**–**	**2,192,988**	**2,192,988**	**0.46**
Vested during the year	**–**	**(55,001)**	**(55,001)**	**5.58**
Forfeited during the year	**–**	**(392,444)**	**(392,444)**	**0.60**
Outstanding at 31 December 2022	**195,000**	**1,868,876**	**2,063,876**	**0.55**

	Performance-based RSUs Number	Time-based RSUs Number	Total RSUs Number	Weighted average grant date fair value per share $
Outstanding at 1 January 2021	464,000	180,000	644,000	8.75
Granted during the year	–	47,500	47,500	4.94
Vested during the year	(89,667)	(41,667)	(131,334)	9.94
Lapsed during the year	(179,333)	(62,500)	(241,833)	10.32
Outstanding at 31 December 2021	195,000	123,333	318,333	6.41

EXPENSE RECOGNISED IN PROFIT OR LOSS

	2022 $'000	2021 $'000
Research and development	**4,962**	7,754
Selling, general and administrative	**6,456**	12,146
	11,418	19,900
By award type		
Restricted share units	**838**	550
Share options	**10,580**	19,350
	11,418	19,900

22 PROVISIONS

	Strimvelis loss provision $000	Dilapidations provision $000	Total $000
Balance at 1 January 2021	4,482	433	4,915
Provisions used during the year	(1,037)	–	(1,037)
Movement in foreign exchange rates	(26)	(5)	(31)
Balance at 31 December 2021	3,419	428	3,847
Balance at 1 January 2022	**3,419**	**428**	**3,847**
Provisions made during the year	**–**	**1,160**	**1,160**
Provisions used during the year	**(274)**	**–**	**(274)**
Movement in foreign exchange rates	**(329)**	**(75)**	**(404)**
Provisions released during the year	**(2,816)**	**–**	**(2,816)**
Balance at 31 December 2022	**–**	**1,513**	**1,513**
Non-current	**–**	**908**	**908**
Current	**–**	**605**	**605**
	–	**1,513**	**1,513**

In April 2018, the Group acquired Strimvelis (ADA-SCID), OTL-200 (MLD), OTL-103 (WAS) and OTL-300 (TDT) from Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD (together, GSK) (the "GSK Transaction"). As part of the GSK transaction, the Group is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Group recorded a provision associated with the loss contract of $18.4 million in 2018, the 'Strimvelis loss provision'.

The provision is an estimate of the expected future losses associated with maintaining the commercial availability of Strimvelis for the required period. The amortization of the provision is recorded as a reduction to research and development expense.

The Group announced its intention to discontinue its investment in Strimvelis in March 2022 and seek alternatives. The future cash flows were reassessed and it was concluded that no further net cash outflow was to be expected following an agreement with a third party to cover ongoing costs.

23 CAPITAL AND RESERVES

SHARE CAPITAL

	Ordinary shares	
In thousands of shares	**2022**	**2021**
In issue at 1 January	**125,674**	98,283
Issued for share options	**1,268**	2,024
Issued as part of a consulting agreement	**5**	23
Issued as part of a collaboration agreement	**–**	1,228
Issuance of shares from private placement	**–**	24,116
In issue at 31 December – fully paid	**126,947**	125,674

	2022 $000	**2021 $000**
Ordinary shares allotted and fully paid, £0.10 nominal value	**16,409**	16,243

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.

SHARE PREMIUM

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

SHARE BASED PAYMENT RESERVE

The share-based payment reserve arises due to the share options issued by the group to its employees within the wider Group.

TRANSLATION RESERVE

The translation reserve comprises all foreign exchange differences arising from the translation of the financial statements of foreign operations.

FAIR VALUE RESERVE

The fair value reserve includes the cumulative net change in the fair value of debt securities measured at FVOCI.

24 FINANCIAL INSTRUMENTS

24 (A) FAIR VALUES OF FINANCIAL INSTRUMENTS

Fair values of financial instruments

The following table shows the carrying amounts and fair value of financial assets and financial liabilities, including their levels in the fair value hierarchy. It does not include fair value for financial assets and financial liabilities not measured at fair value if the carrying amount is reasonable approximation of fair value.

The Group believes that the carrying amount reflected on the consolidated statement of financial position for cash and cash equivalents, trade and other receivables, and trade and other payables approximate fair value due to their short-term maturities. The carrying value of the Group's outstanding Term Loan and lease liabilities approximates fair value (a Level 2 fair value measurement), as they reflect interest rates currently available to the Group. There are therefore no financial liabilities which require inclusion in the table below.

31 December 2022	Carrying value Total $000	Fair value Level 1 $000	Fair value Level 2 $000	Fair value Total $000
Financial assets				
Debt securities within recognised as part of cash and cash equivalents (note 18)	**27,161**	**1,239**	**25,922**	**27,161**
Short-term investments (note 15)	**75,326**	**–**	**75,326**	**75,326**
	102,487	**1,239**	**101,248**	**102,487**

31 December 2021	Carrying value Total $000	Fair value Level 1 $000	Fair value Level 2 $000	Fair value Total $000
Financial assets				
Debt securities within recognised as part of cash and cash equivalents	41,604	21,085	20,519	41,604
Short-term investments (note 15)	164,195	–	164,195	164,195
	205,799	21,085	184,714	205,799

Fair values hierarchy

Level 1: quoted prices (unadjusted) in active markets for identical assets or liabilities

Level 2: inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly (i.e., as prices) or indirectly (i.e., derived from prices)

Level 3: inputs for the asset or liability that are not based on observable market data (unobservable inputs).

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

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

24 FINANCIAL INSTRUMENTS *continued*

24 (B) CREDIT RISK

The Group 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 Group to concentrations of credit risk consist primarily of cash, cash equivalents, short-term investments and receivables including restricted cash.

The Group invests its excess cash, in line with its investment policy, in money market funds and high credit quality debt instruments. The Group's cash is deposited in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships or entities for which it has a receivable.

24 (C) LIQUIDITY RISK

Liquidity risk is the risk that the Group will not be able to meet its financial obligations as they fall due. The Group's objective when managing liquidity is to ensure, as far as possible, that it will have sufficient liquidity to meet its liabilities when they are due, under both normal and stressed conditions, without incurring unacceptable losses or risk damaged to the Group's reputation.

The Group currently has $33.0 million of principal indebtedness outstanding under the senior term facilities agreement, or the Amended Credit Facility, with MidCap Financial (Ireland) Limited. The Group has the ability to borrow up to an additional $67.0 million in the future under the Amended Credit Facility upon satisfaction of certain conditions. The existing indebtedness and any additional indebtedness the Group may incur could require us to divert funds identified for other purposes for debt service and impair the Group's liquidity position.

24 FINANCIAL INSTRUMENTS *continued*

The table below set outs the contractual maturities of the Group's financial instruments at the reporting date. The amounts are gross and undiscounted, and include estimated contractual interest payments and exclude the effect of netting agreements.

	Carrying value	Contractual cash flows				
31 December 2022	Total $000	Total $000	1 year or less $000	1 to <2years $000	2 to <5years $000	5 years and over $000
Financial assets						
Cash and cash equivalents	**68,424**	**68,424**	**68,424**	**–**	**–**	**–**
Trade and other receivables	**16,436**	**16,436**	**16,436**	**–**	**–**	**–**
Lease receivables	**14,199**	**18,363**	**2,246**	**2,313**	**7,372**	**6,432**
Short-term investments	**75,326**	**75,326**	**75,326**	**–**	**–**	**–**
	174,385	**178,549**	**162,432**	**2,313**	**7,372**	**6,432**
Financial liabilities						
Trade and other payables	**(45,498)**	**(45,498)**	**(41,888)**	**(520)**	**(520)**	**(2,570)**
Lease liabilities	**(25,670)**	**(40,373)**	**(6,517)**	**(6,972)**	**(14,618)**	**(12,266)**
Borrowings	**(32,665)**	**(33,371)**	**(9,429)**	**(9,429)**	**(14,513)**	–
	(103,833)	**(119,242)**	**(57,834)**	**(16,921)**	**(29,651)**	**(14,836)**
Total	**70,552**	**59,307**	**104,598**	**(14,608)**	**(22,279)**	**(8,404)**

	Carrying value	Contractual cash flows				
31 December 2021	Total $000	Total $000	1 year or less $000	1 to <2years $000	2 to <5years $000	5 years and over $000
Financial assets						
Cash and cash equivalents	55,912	55,912	55,912	–	–	–
Trade and other receivables	18,370	18,370	18,370	–	–	–
Lease receivables	15,343	20,543	2,180	2,246	7,150	8,967
Short-term investments	164,195	164,195	164,195	–	–	–
	253,820	259,020	240,657	2,246	7,150	8,967
Financial liabilities						
Trade and other payables	(34,524)	(34,524)	(31,954)	–	–	(2,570)
Lease liabilities	(26,613)	(41,311)	(7,326)	(6,773)	(15,880)	(11,332)
Borrowings	(33,203)	(34,155)	(786)	(9,429)	(23,940)	–
	(94,340)	(109,990)	(40,066)	(16,202)	(39,820)	(13,902)
Total	159,480	149,030	200,591	(13,956)	(32,670)	(4,935)

24 FINANCIAL INSTRUMENTS *continued*

24 (D) MARKET RISK

Financial risk management

Market risk is the risk that changes in market prices, such as foreign exchange rates, interest rates and equity prices will affect the Group's income or the value of its holdings of financial instruments

Market risk - Foreign currency risk

The Group is exposed to foreign currency exchange risk because it currently operates in the United Kingdom and the United States. The reporting currency of the Group is the U.S. dollar. The Group 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 statement of financial position 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. The Group recorded realised and unrealised foreign currency losses of $24.3 million for the year ended 31 December 2022 (2021: $1.1 million) These foreign currency transaction gains and losses are included in the consolidated statements of profit or loss and comprehensive loss.

Assets and liabilities have been translated at the exchange rates at the statement of financial position dates, while revenue and expenses are translated at the average exchange rates over the reporting period and shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net loss but are included in the translation reserve, a separate component of equity.

The Group does not currently engage in currency hedging activities in order to reduce the currency exposure, but it 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.

Foreign currency exchange rates

The following significant exchange rates have been applied:

	Average rate		Year-end spot rate	
	2022 $000	**2021 $000**	**2022 $000**	**2021 $000**
Sterling	**1.2438**	1.3342	**1.2103**	1.3497
Euros	**1.0584**	1.1335	**1.0736**	1.1318

24 FINANCIAL INSTRUMENTS *continued*

Sensitivity analysis

A 10 percent weakening of the following currencies against the U.S. Dollar at 31 December 2022 would have increased loss after taxation by the amounts shown below. This calculation assumes that the change occurred at the statement of financial position date and had been applied to risk exposures existing at that date.

This analysis assumes that all other variables, in particular other exchange rates and interest rates, remain constant. The analysis is performed on the same basis for the year ended 31 December 2021.

	Profit or loss	
	2022	**2021**
	$000	**$000**
Sterling	**(24,497)**	(6,363)
Euros	**(1,750)**	(1,867)

A 10 percent strengthening of the above currencies against the U.S. Dollar at 31 December 2022 would have had the equal but opposite effect on the above currencies to the amounts shown above, on the basis that all other variables remain constant.

Market risk – Interest rate risk

As of 31 December 2022, the Group had cash, cash equivalents, short-term investments and restricted cash of $148.0 million. The Group's exposure to interest rate sensitivity is impacted by changes in the underlying UK and U.S. bank interest rates. The Group's 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, an immediate one percentage point change in interest rates would not have a material effect on the fair market value of the Group's portfolio, and therefore neither operating results or cash flows are expected to be significantly affected by changes in market interest rates.

The Group has borrowed $33.0 million under its credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 5.95% plus LIBOR. As of 31 December 2022, the carrying value of the Term Loans under the credit facility was $32.7 million.

In 2017, the United Kingdom's Financial Conduct Authority announced that after 2021 it would no longer compel banks to submit the rates required to calculate the London Interbank Offered Rate (LIBOR) and other interbank offered rates, which have been widely used as reference rates for various securities and financial contracts, including loans, debt and derivatives. 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). At 31 December 2022 the Group's credit facilities referenced LIBOR-based rates. In January 2023, the Group amended and restated our credit facility to change from LIBOR to SOFR. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

24 FINANCIAL INSTRUMENTS *continued*

The table below sets outs the interest rate profile of the Group's interest-bearing financial instruments:

		2022 $000	2021 $000
Fixed rate instruments			
Lease receivables	25	**14,199**	15,343
Lease liabilities	18	**(25,670)**	(26,613)
		(11,471)	(11,270)
Variable rate instruments			
Cash and cash equivalents		**68,424**	55,912
Short-term investments		**75,326**	164,195
Term Loan	18	**(32,655)**	(33,203)
		111,095	186,904

Fixed-rate instruments are measured at amortised cost, therefore, a change in interest rate at the reporting date would not affect profit or loss.

A change of 100 basis points in interest rates at the statement of financial position date would have increased or decreased equity by $0.3 million (2021: $0.3 million). This calculation assumes that the change occurred at the statement of financial position date and had been applied to risk exposures existing at that date. This analysis assumes that all other variables, in particular foreign currency rates, remain constant and considers the effect of financial instruments with variable interest rates.

24 (E) CAPITAL MANAGEMENT

The Group's capital management objective is to ensure the Group's ability to continue as a going concern so that it can provide returns for shareholders and benefits for other stakeholders. To meet this objective the Group reviews the budgets and forecasts on a regular basis to ensure there is sufficient capital to meet the needs of the Group.

The capital structure of the Group consists of total parent shareholders' equity as set out in the Consolidated Statement of Changes in Equity.

To date, the Group has financed its operations primarily with proceeds from the sale of ADSs in the IPO and follow-on offering, proceeds from the sale of ordinary shares in the private placement, proceeds from the sale of convertible preferred shares, reimbursements associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program, upfront payments from our collaboration agreement with Pharming Group N.V., our Original Credit Facility and our Amended Credit Facility with MidCap, and through proceeds from sales of Libmeldy in Europe beginning in 2022.

25 LEASES

25 (A) LEASES AS A LESSEE

The Group leases office and laboratory space in London, United Kingdom and Boston, Massachusetts, United States. The Group's facility leases generally contain customary provisions allowing the landlords to terminate the leases if the Group fails to remedy a breach of any obligations under any such lease within specified time periods, or upon bankruptcy or insolvency. The leases do not include any restrictions or covenants that had to be accounted for under the lease guidance.

25 LEASES *continued*

Right-of-use assets

	Land and buildings $000
Net book values	
Balance at 1 January 2021	18,746
Additions to right-of-use assets	535
Depreciation charge for the year	(4,523)
Modification or remeasurement of the lease liability	(664)
Movement in foreign exchange rates	(221)
Balance at 31 December 2021	13,873
Additions to right-of-use assets	6,248
Depreciation charge for the year	(4,367)
Modification or remeasurement of the lease liability	(1,791)
Movement in foreign exchange rates	(1,194)
Balance at 31 December 2022	12,769

Amounts recognised in profit or loss

The following amounts have been recognised in profit or loss for which the Group is a lessee:

	2022 $000	2021 $000
Interest expense on lease liabilities	**2,260**	3,302
Expenses relating to variable lease payments not included in the measurement of lease liabilities	**1,602**	1,696

Amounts recognised in statement of cash flows

	2022 $000	2021 $000
Repayment of capital	**5,218**	5,523
Repayment of interest	**2,260**	3,302
Total cash outflow for leases	**7,478**	8,825

Information on lease liabilities is disclosed in note 19.

25 LEASES *continued*

25 (B) LEASES AS A LESSOR

Fremont sublease agreements

In December 2018, the Group 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 Group committed to a restructuring plan whereby we ceased construction and build-out of the Fremont facility. In December 2020, the Group entered into a sublease agreement (the "Sublease") with an unrelated third-party (the "subtenant") whereby the Group subleased the entire Fremont facility to the subtenant. The Group accounts for the Head Lease and Sublease as two separate contracts. The Sublease commenced in December 2020 and is in force for the remainder of the Head Lease term, through May 2030. The Sublease is assessed to be a finance lease under IFRS 16 as risk and rewards incidental to ownership of the underlying right-of-use asset arising from the Head Lease have substantially been transferred to the sublessee.

The following amounts have been recognised in profit or loss in respect of the sublease:

	2022 $000	2021 $000
Interest income on lease receivables	**1,037**	1,057

The following table sets out a maturity analysis of lease payments receivable, showing the undiscounted lease payments to be received after the reporting date:

	2022 $000	2021 $000
Less than one year	**2,246**	2,180
Between one and two years	**2,313**	2,246
Between two and three years	**2,382**	2,313
Between three and four years	**2,454**	2,382
Between four and five years	**2,535**	2,454
More than five years	**6,432**	8,968
Total undiscounted lease receivable	**18,362**	20,543
Unearned finance income	**(4,163)**	(5,200)
Net investment in the lease	**14,199**	15,343
Amounts due within one year	**1,294**	1,143
Amounts due in more than one year	**12,905**	14,200
Net investment in the lease	**14,199**	15,343

26 COMMITMENTS

Manufacturing and technology development master agreement with AGC Biologics S.pA. ("AGC")

On 2 July 2020, the Group entered into the AGC Agreement pursuant to which AGC will develop, manufacture, and supply certain viral vectors and conduct cell processing activities for certain Group development and commercial programs. Under the terms of the AGC Agreement, the Group 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 31 December 2022:

	Product manufacturing commitments $000	Dedicated manufacturing and development resources[1] $000	Exclusive transduction suites[2] $000	Total AGC Commitment $000
Due in:				
2023	1,933	5,655	2,147	9,735
2024	1,933	5,655	2,147	9,735
2025	966	2,827	1,074	4,867
Total manufacturing commitments	4,832	14,137	5,368	24,337

The following table outlines the annual commitments associated with the contract as of 31 December 2021:

	Product manufacturing commitments $000	Dedicated manufacturing and development resources[1] $000	Exclusive transduction suites[2] $000	Total AGC Commitment $000
Due in:				
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
Total manufacturing commitments	10,254	27,956	10,323	48,533

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

(1) The Group 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.

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

The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending 2 July 2025. The agreement may be extended for an additional two years by mutual agreement of the Group and AGC.

26 COMMITMENTS *continued*

The Group incurred $13.7 million and $16.4 million in expenses related to the AGC Agreement in the years ended 31 December 2021 and 2022, respectively. The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending 2 July 2025. The AGC Agreement may be extended for an additional two years by mutual agreement of the Group and AGC. The Group 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 2 July 2022, AGC has the right to terminate the AGC Agreement at its discretion upon 24-month's prior written notice to the Group. 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 Group has entered into several license agreements outlined below. In connection with these agreements the Group is required to make milestone payments and annual license maintenance payments or royalties on future sales of specified products.

GSK asset purchase and license agreement

In April 2018, the Group completed an asset purchase and license agreement (the "GSK Agreement") with subsidiaries of GSK to acquire a portfolio of autologous ex vivo gene therapy assets and licenses for rare diseases and option rights on three additional programs in pre-clinical development from Telethon Foundation and San Raffaele Hospital ("Telethon-OSR"). The portfolio of approved and investigational rare disease gene therapies included Strimvelis and OTL-200 for MLD, among other programs. GSK also simultaneously novated to us their R&D Agreement with Telethon-OSR.

The Group accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business combination, resulting in total consideration of $133.6 million, which was recorded in 2018.

The Group is also required to use commercially reasonable efforts to obtain a priority review voucher, or PRV, from the FDA for certain programs, including OTL-200, and to transfer the first such PRV to GSK. GSK also has an option to acquire at a defined price any PRVs granted to the Group thereafter for certain programs. In the event that GSK does not exercise this option with respect to any PRV, the Group may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As part of the GSK Agreement the Group is also required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site.

Under the GSK Agreement the Group is also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. For example, for Libmeldy, the Group pays a tiered royalty rate at percentages from the mid-teens to the low twenties. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Group may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones applicable to GSK. The Group's royalty obligations with respect to OTL-200 may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Group'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 and OTL-200, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition or through 31 December 2022, and are not included as part of consideration.

26 COMMITMENTS *continued*

Telethon-OSR research and development collaboration and license agreements

In connection with the Group's entering into the GSK Agreement in April 2018, the Group also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous ex vivo gene therapies for ADA-SCID, WAS, MLD and TDT.

As consideration for the licenses, the Group will be required to make payments to Telethon-OSR upon achievement of certain product development milestones, up to an aggregate of approximately €31.0 million ($33.4 million at 31 December 2022). Additionally, the Group will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses of the collaboration programs.

In May 2019, the Group entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Group an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's ex vivo autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I, including the Hurler variant ("MPS-IH"). Under the terms of the agreement, Telethon-OSR received €15.0 million in upfront and milestone payments from the Group upon entering into the agreement. The Group is also required to pay up to €28.0 million ($30.1 million at 31 December 2022) related to milestone payments contingent upon achievement of certain development, regulatory and commercial milestones. Additionally, the Group 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 Group completed the UCLB/UCLA license agreement, under which the Group 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 Group 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 Group 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 Group recorded research and development expenses based on the fair value of the ordinary shares as of the time the agreement was executed or modified.

Under the UCLB/UCLA License Agreement, the Group may become obligated to make payments to the parties of up to an aggregate of £19.9 million ($24.1 million at 31 December 2022) upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

In June 2021, the Group terminated the license to its OTL-101 program for ADA-SCID, which was granted pursuant to the UCLB/UCLA license agreement. Except for the termination of such license, the UCLB/UCLA license agreement continues in full force and effect. Unless terminated earlier by either party, the UCLB/UCLA license agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, and amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Group entered into an arrangement with Oxford BioMedica plc whereby Oxford BioMedica granted an exclusive intellectual property license to the Group for the purposes of

26 COMMITMENTS *continued*

research, development, and commercialization of collaboration products, and whereby Oxford BioMedica will provide process development services ("Oxford BioMedica Development Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Development Agreement, the Group issued 588,220 ordinary shares to Oxford BioMedica. The Group 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 Group 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 Group 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 Group issued another 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million which was recorded to research and development expense. No milestones were met during the year ended 31 December 2022. The Group may also pay low single-digit percentage royalties on net sales of collaborated products generated under the Oxford BioMedica Agreement.

Legal proceedings

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

Indemnification agreements

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

27 RELATED PARTY TRANSACTIONS

TRANSACTIONS WITH KEY MANAGEMENT PERSONNEL

Directors of the Parent Company and their immediate relatives control 0.4% (2021: 0.4%) per cent of the voting shares of the Company.

The compensation of key management personnel (including the directors) is as follows:

	2022 $000	2021 $000
Key management remuneration including social security costs	**2,165**	2,083
Company contributions to money purchase pension schemes	**12**	12
Equity settled share-based payments	**3,206**	5,941
	5,383	8,036

ULTIMATE CONTROLLING PARTY

There is no ultimate controlling party of the Group as ownership is split between the Group's shareholders.

28 SUBSEQUENT EVENTS

RATIO CHANGE

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

ISSUANCE OF SHARES THROUGH 2023 PRIVATE PLACEMENT

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

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

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

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

The second closing is expected to occur on the fifth trading day after the Group notifies the purchasing parties that the Second Closing Trigger has occurred and is subject to additional, customary closing conditions. If the Second Closing Trigger occurs, the Group anticipates receiving gross proceeds of approximately $34.0 million from the second closing of the 2023 Private Placement, before deducting fees to the placement agent and other offering expenses payable by the Group.

28 SUBSEQUENT EVENTS *continued*

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

29 EXPLANATION OF TRANSITION TO UK-ADOPTED IFRS

As stated in note 1, these are the Group's first consolidated financial statements prepared in accordance with UK-adopted IFRSs.

The accounting policies set out in note 1 have been applied in preparing the financial statements for the year ended 31 December 2022, the comparative information presented in these financial statements for the year ended 31 December 2021 and in the preparation of an opening IFRS Consolidated statement of financial position at 1 January 2021(the Group's date of transition).

In preparing its opening IFRS Consolidated statement of financial position, the Group has adjusted amounts reported previously in financial statements prepared in accordance with its previous basis of accounting (US GAAP). An explanation of how the transition from US GAAP to UK-adopted IFRSs has affected the Group's financial performance, financial position and cash flows is set out in the following tables and the notes that accompany the tables.

29 EXPLANATION OF TRANSITION TO UK-ADOPTED IFRS *continued*

RECONCILIATION OF TOTAL COMPREHENSIVE LOSS FOR 2021

	Note	US GAAP $000	Effect of transition to UK-adopted IFRSs $000	UK-adopted IFRSs $000
Product sales		700	–	700
Collaboration revenue		975	–	975
Total revenue		1,675	–	1,675
Cost of sales		(226)	–	(226)
Gross profit		1,449	–	1,449
Research and development expense	*c, d, f*	(86,977)	(66,668)	(153,645)
Selling, general and administrative expense	*a, b, c, d*	(54,905)	3,058	(51,847)
Other operating income and expense		(90)	–	(90)
Net foreign exchange loss		(1,148)	–	(1,148)
Operating loss		(141,671)	(63,610)	(205,281)
Finance income	*b*	412	1,057	1,469
Finance expenses	*a*	(2,497)	(3,302)	(5,799)
Net finance expense		(2,085)	(2,245)	(4,330)
Loss before tax		(143,756)	(65,855)	(209,611)
Taxation	*f*	(828)	12,164	11,336
Loss for the year		(144,584)	(53,691)	(198,275)
Foreign currency translation differences – foreign operations		3,124	(2,027)	1,097
Net change in fair value of debt investments at fair value through other comprehensive income		(251)	–	(251)
Tax on items that may be classified subsequently to statement of profit or loss				
Other comprehensive loss, net of income tax		2,873	(2,027)	846
Total comprehensive loss for the year		(141,711)	(55,718)	(197,429)

29 EXPLANATION OF TRANSITION TO UK-ADOPTED IFRS *continued*

RECONCILIATION OF EQUITY

	Note	1 January 2021 US GAAP $000	1 January 2021 Effect of transition to UK-adopted IFRSs $000	1 January 2021 UK-adopted IFRSs $000	31 December 2021 US GAAP $000	31 December 2021 Effect of transition to UK-adopted IFRSs $000	31 December 2021 UK-adopted IFRSs $000
Non-current assets							
Property, plant and equipment		4,781	–	4,781	**4,767**	**–**	**4,767**
Right-of-use assets	*a, b*	29,815	(11,069)	18,746	**24,316**	**(10,443)**	**13,873**
Intangible assets	*c*	3,076	117,123	120,199	**4,149**	**59,259**	**63,408**
Lease receivable	*b*	–	14,466	14,466	–	**14,200**	**14,200**
Other receivables	*b*	14,511	(1,553)	12,958	**9,770**	**(3,407)**	**6,363**
Deferred tax assets	*e*	5,219	13,468	18,687	**4,086**	**(973)**	**3,113**
		57,402	132,435	189,837	**47,088**	**58,636**	**105,724**
Current assets							
Inventories		665	–	665	**2,015**	**–**	**2,015**
Lease receivable	*b*	–	–	–	**–**	**1,143**	**1,143**
Trade and other receivables	*b*	13,577	(39)	13,538	**22,475**	**(40)**	**22,435**
Research and development tax credit receivable		17,344		17,344	**30,723**	**–**	**30,723**
Short-term investments		136,813	–	136,813	**164,195**	**–**	**164,195**
Cash and cash equivalents		55,135	–	55,135	**55,912**	**–**	**55,912**
		223,534	(39)	223,495	**275,320**	**1,103**	**276,423**
Total assets		280,936	132,396	413,332	**322,408**	**59,739**	**382,147**
Current liabilities							
Loans and borrowings		4,861	–	4,861	**786**	**–**	**786**
Lease liabilities		8,934	–	8,934	**7,335**	**–**	**7,335**
Trade and other payables		36,850	–	36,850	**33,655**	**–**	**33,655**
Deferred income		–	–	–	**346**	**–**	**346**
Provisions		916	–	916	**671**	**–**	**671**
		51,561	–	51,561	**42,793**	**–**	**42,793**
Non-current liabilities							
Loans and borrowings		20,204	–	20,204	**32,086**	**–**	**32,086**
Lease liabilities		24,168	–	24,168	**19,278**	**–**	**19,278**
Other payables		2,571	–	2,571	**2,607**	**–**	**2,607**
Deferred income		–	–	–	**12,519**	**–**	**12,519**
Provisions		3,999	–	3,999	**3,176**	**–**	**3,176**
		50,942	–	50,942	**69,666**	**–**	**69,666**
Total liabilities		102,503	–	102,503	**112,459**	**–**	**112,459**
Net assets		178,433	132,396	310,829	**209,949**	**59,739**	**269,688**
Equity attributable to equity holders of the parent							
Share capital		12,497	–	12,497	**16,243**	**–**	**16,243**
Share premium		339,435	–	339,435	**486,382**	**–**	**486,382**
Translation reserve	*g*	293	–	293	**3,417**	**(2,028)**	**1,389**
Share-based payment reserve	*g*	55,417	27,297	82,714	**77,951**	**10,358**	**88,309**
Fair value reserve		80	–	80	**(171)**	**–**	**(171)**
Retained earnings		(229,289)	105,099	(124,190)	**(373,873)**	**51,409**	**(322,464)**
Total equity		178,433	132,396	310,829	**209,949**	**59,739**	**269,688**

29 EXPLANATION OF TRANSITION TO UK-ADOPTED IFRS *continued*

Notes to the reconciliation of equity and loss

a The Group elected to adopt IFRS 16 using the practical expedient permitted under IFRS 1 to initially measure the right-of-use asset at an amount equal to the lease liability as at the date of transition, being 1 January 2021. Subsequent to its initial recognition, the right-of-use asset is amortised under IFRS 16 on a straight-line basis over the lease term. Under US GAAP, the Group's leases were classified as operating leases; the amortisation charge was, therefore, calculated as the total lease payment less interest for the period. The interest payable on lease liabilities is presented as a finance expense as opposed to an operating expense under US GAAP.

b Under US GAAP, a lessor classifies a sublease as either a finance or operating lease with reference to the underlying lease assets. Under IFRS 16, a lessor classifies a sublease as either a finance or operating lease with reference to the right-of-use asset arising from the head lease. The Fremont sublease has been classified as a finance lease under IFRS 16; consequently, the right-of-use asset associated with the headlease has been derecognised and a finance lease receivable recognised in respect of this sublease arrangement. Under US GAAP, the sublease was classified as an operating lease with the lease income received recognised directly in the Consolidated statement of profit or loss on a straight-line basis.

c Under US GAAP, the Group expensed acquired research and development assets as no alternative future use was identified. Under IFRS, the probability recognition criterion for intangibles assets under IAS 38 is always considered to be met for separately acquired intangible assets as the price paid reflects expectations about the probability that future economic benefits of the asset will flow to the entity. Consequently, the Group has recognised additional intangible assets under IAS 38 in relation to externally acquired licenses used in the Group's research and development activities. Subsequent to their initial recognition, these licenses are measured at cost less accumulated amortisation and impairment.

d The Group has granted Share Options to employees and directors of the Group with various vesting schedules which are capable of being exercised as they vest in monthly tranches over a period of three to four years from the grant date. Under US GAAP, the Group measured the awards granted to employees based on the fair value on the date of grant and recognised a compensation expense on a straight-line basis over the vesting period. Under IFRS 2, each tranche is accounted for as a separate share-based payment. The Group has determined and adjusted the fair value, and associated share-based payment expense recognised, for all options with monthly vesting which remain outstanding from the date of transition.

e Under US GAAP, the Group recorded deferred tax on its equity-settled share options based on the amount of share-based payment expense recognised. Changes in share price do not impact the deferred tax asset recognised. Under IAS 12, deferred tax is recognised on equity-settled share options based on an estimate of future tax deduction for the award measured at each reporting period. Where the tax deduction is based on a future share price, the estimate is based on the current share price.

In addition to this, the deferred tax impact of GAAP adjustments identified has been recognised primarily in respect of share-based payments.

f Under US GAAP, the Group recognised investment tax credits received under the SME regime as operating income. Under IFRS, as the tax credits are linked to taxable losses, these are recognised under the scope of IAS 12 and are recognised as part of income tax expense.

g The impact of GAAP adjustments set out in *a to f* above arising in foreign operations, primarily in Orchard Therapeutics (Europe) Limited, on the foreign currency translation reserve has been calculated and recognised.

EXPLANATION OF MATERIAL ADJUSTMENTS TO THE CASH FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2021

Under IFRS 16, the Group has elected to present lease payments made as a lessee as a financing cash flow. Under US GAAP, lease payments made by the group as a lessee were recognised as an operating cash flow.

Under IFRS 16, the sublease has been assessed to be a finance lease is classified as an investing cash flow. Under US GAAP, the sublease was an operating lease and the associated cash inflows were recognised as an operating cash flow.

Under US GAAP, research and development tax credit receivable under the SME scheme was recognised as operating income. Under IFRS, this is recognised within income tax, and the associated in flow cash flows presented as part of tax paid/received.

There was no overall impact to the total change in net cash during the year as a result of the transition.

ORCHARD THERAPEUTICS PLC
PARENT COMPANY FINANCIAL STATEMENTS
FOR THE YEAR ENDED 31 December 2022

Parent Company Balance Sheet

at 31 December 2022

	Note	2022 $000	2021 $000
Fixed assets			
Investments in subsidiaries	3	**–**	–
Current assets			
Debtors	4	**1,669**	20,434
Short-term investments	5	**50,918**	147,996
Cash and cash equivalents		**27,474**	35,809
		80,061	204,239
Current liabilities			
Creditors: amounts falling due within one year	6	**(11,207)**	(1,606)
Net current assets		**68,854**	202,633
Total assets less current liabilities		**68,854**	202,633
Non-current liabilities			
Creditors: amounts falling due after more than one year	6	**(22,991)**	(32,086)
Net assets		**45,863**	170,547
Equity			
Share capital	8	**16,409**	16,243
Share premium	8	**486,405**	486,382
Share-based payment reserve	8	**98,941**	87,523
Other comprehensive income	8	**(121)**	(137)
Accumulated losses	8	**(555,771)**	(419,464)
Equity attributable		**45,863**	170,547

The Company has elected to take the exemption under section 408 of the Companies Acts 2006 from presenting the Company Statement of Comprehensive Income. The Company loss for the year ended 31 December 2022 was a loss of $136.3 million (2021: loss of $428.5 million).

These Parent Company financial statements were approved by the board of directors on 27 April 2023 and were signed on its behalf by:

Hubert Gaspar
Director
27 April 2023
Company registered number: 11494381

Parent Company Statement of Changes in Equity

for the year ended 31 December 2022

	Share capital $000	Share premium $000	Share-based payment reserve $000	Other comprehensive income $000	Retained earnings $000	Total Equity $000
Balance at 1 January 2022	**16,243**	**486,382**	**87,523**	**(137)**	**(419,464)**	**170,547**
Total comprehensive loss for the year						
Loss for the year	**–**	**–**	**–**	**–**	**(136,307)**	**(136,307)**
Other comprehensive income	**–**	**–**	**–**	**16**	**–**	**16**
Total comprehensive loss for the year	**–**	**–**	**–**	**16**	**(136,307)**	**(136,291)**
Transactions with owners, recorded directly in equity						
Issue of shares under employee equity plans	**166**	**24**	**–**	**–**	**–**	**190**
Issue of shares under consulting agreements	**–**	**(1)**	**–**	**–**	**–**	**(1)**
Share-based compensation expense	**–**	**–**	**11,418**	**–**	**–**	**11,418**
Total transactions with owners	**166**	**23**	**11,418**	**–**	**–**	**11,607**
Balance at 31 December 2022	**16,409**	**486,405**	**98,941**	**(121)**	**(555,771)**	**45,863**

	Share capital $000	Share premium $000	Share-based payment reserve $000	Other comprehensive income $000	Retained earnings $000	Total Equity $000
Balance at 1 January 2021	12,497	339,435	67,623	83	9,056	428,694
Total comprehensive loss for the year						
Loss for the year	–	–	–	–	(428,520)	(428,520)
Other comprehensive loss	–	–	–	(220)	–	(220)
Total comprehensive loss for the year	–	–	–	(220)	(428,520)	(428,740)
Transactions with owners, recorded directly in equity						
Issue of shares under employee equity plans	263	2,650	–	–	–	2,913
Issue of shares under collaboration agreements	170	3,965	–	–	–	4,135
Issue of shares under consulting agreements	3	(3)	–	–	–	–
Issue of shares from private placement	3,310	146,690	–	–	–	150,000
Share issue costs	–	(6,355)	–	–	–	(6,355)
Share-based compensation expense	–	–	19,900	–	–	19,900
Total transactions with owners	3,746	146,947	19,900	–	–	170,593
Balance at 31 December 2021	16,243	486,382	87,523	(137)	(419,464)	170,547

1 ACCOUNTING POLICIES

1.1 NATURE OF BUSINESS

The Company is a public limited company incorporated pursuant to the laws of England and Wales. The registered number is 11494381 and the registered address is 245 Hammersmith Road, 3rd Floor, London, England, W6 8PW, United Kingdom.

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 utilises 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 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 31 October 2018. As at 31 December 2022 the Company's ADSs each represent one ordinary share of the Company, following the ratio change on 10 March 2023 each ADS represents 10 ordinary shares of the Company (see note 11).

On 9 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 4 February 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 4 February 2021. At 31 December 2021 all outstanding non-voting shares have been converted to voting ordinary shares.

On 10 March 2023, the Company issued and sold (i) 56,666,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share and (ii) warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per ten shares and accompanying warrant, in an unregistered offering (together (i) and (ii) the "2023 Private Placement"). The 2023 Private Placement resulted in gross proceeds of approximately $34.0 million. The ordinary shares, non-voting ordinary shares, and warrants were sold pursuant to a securities purchase agreement entered into between the Company and the purchasers named therein on 6 March 2023.

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

1.2 BASIS OF PREPARATION

These financial statements were prepared in accordance with Financial Reporting Standard 101 *Reduced Disclosure Framework* ("FRS 101").

In preparing these financial statements, the Company applies the recognition, measurement and disclosure requirements of UK-adopted international accounting standards ("UK-adopted IFRS"), but makes amendments where necessary in order to comply with Companies Act 2006 and has set out below where advantage of the FRS 101 disclosure exemptions has been taken.

The financial statements were historically prepared in accordance with UK GAAP, Financial Reporting Standard 102. In the transition to FRS 101, the Company has applied IFRS 1 whilst ensuring that its assets and liabilities are measured in compliance with FRS 101. An explanation of how the transition to FRS 101 has affected the reported financial position and financial performance of the Company is provided in note 13.

IFRS 1 grants certain exemptions from the full requirements of UK-adopted IFRSs in the transition period. The following exemptions have been taken in these financial statements:

Recognise, as permitted under IFRS 1.D15, the carrying amount of the Company's investment in ordinary shares held in Orchard Therapeutics (Europe) Limited at the date of transition at deemed cost, being the previous GAAP carrying amount at this date.

The Company is included in the consolidated financial statements of Orchard Therapeutics plc, which are prepared in accordance with UK-adopted IFRS and are included within this Annual Report.

In these financial statements, the Company has applied the exemptions available under FRS 101 in respect of the following disclosures:

- Cash Flow Statement and related notes;
- Comparative period reconciliations for share capital;
- Disclosures in respect of transactions with wholly owned subsidiaries;
- Disclosures in respect of capital management;
- The effects of new but not yet effective IFRSs;
- An additional balance sheet for the beginning of the earliest comparative period following the retrospective change in accounting policy; and
- Disclosures in respect of the compensation of Key Management Personnel.

As the consolidated financial statements of Orchard Therapeutics plc include the equivalent disclosures, the Company has also taken the exemptions under FRS 101 available in respect of the following disclosures:

- IFRS 2 Share-Based Payments in respect of group settled share-based payments
- Certain disclosures required by IFRS 13 Fair Value Measurement and the disclosures required by IFRS 7 Financial Instrument Disclosures.

The accounting policies set out below have, unless otherwise stated, been applied consistently to all periods presented in these financial statements.

Judgements made by the directors, in the application of these accounting policies that have a significant effect on the financial statements and estimates with a significant risk of material adjustment in the next year are discussed in note 2.

1.3 MEASUREMENT CONVENTION

The financial statements are prepared on the historical cost basis modified by the revaluation of certain items, as stated in the accounting policies and on a going concern basis.

The Company's financial statements are presented in US dollars, which is the Company's functional currency.

Amounts reported are based in thousands, except percentages, per share amounts or as otherwise noted.

1.4 GOING CONCERN

The Company expects that its cash, cash equivalents, and short-term investments as of 31 December 2022, of $78.4 million, together with the $34 million received in March 2023 from the 2023 Private Placement (see note 28 to the Consolidated financial statements), will be sufficient to fund its operations and capital expenditure requirements, as well as those of the wider Group, for at least twelve months from the date of signing of this Annual Report and Financial Statements. Management have prepared a budget to support the going concern assumption of the Company which shows the Company has sufficient resources to continue as a going concern into 2025.

1.5 INVESTMENTS IN SUBSIDIARIES

The investment in the subsidiary arose on the reorganization of the Group in 2018. Investments in subsidiaries are carried at cost less impairment. On transition to FRS 101 on 1 January 2021, the Company elected to recognised investments in subsidiaries at deemed cost, being the previous GAAP carrying amount on this date. The Company recognises 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.

1.6 FOREIGN CURRENCY

Transactions in foreign currencies are translated to the Company's functional currencies at the foreign exchange rate ruling at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are translated to the functional currency at the foreign exchange rate ruling at that date. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction. Foreign exchange differences arising on translation are recognised in the profit and loss account.

1.7 FINANCIAL INSTRUMENTS

The Company's financial instruments include amounts owed by subsidiary undertakings, trade creditors, cash and cash equivalents, borrowings, and short-term investments.

Cash and cash equivalents

Cash and cash equivalents comprise cash balances, deposits held at call with banks and short-term highly liquid investments purchased with original maturities of 90 days or less at the date of acquisition.

Intercompany receivables

Receivables due from other group companies for services performed in the ordinary course of business are recognised initially at fair value and subsequently measured at amortised cost using the effective interest method, less any impairment losses. The Company applies IFRS 9 to measuring expected credit losses on all intercompany receivables (see note 2).

1.7 FINANCIAL INSTRUMENTS *continued*

Trade creditors

Trade creditors represent 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.

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 investments represent the investment of cash that is available for current operations

Short-term investments have been classified as measured at fair value through other comprehensive income 'FVOCI' as a) they are held within a business model whose objective is achieved by both collecting contractual cash flows and selling financial assets; and b) their contractual terms give rise on specified dates to cash flows that are solely payments of principal and interest on the principal amount outstanding.

Short-term investments in debt securities are subsequently measured at fair value. Interest income calculated using the effective interest method, foreign exchange gains and losses and impairment are recognised in profit or loss. Other net gains and losses are recognised in other comprehensive income 'OCI'. On derecognition, gains and losses accumulated in OCI are reclassified to profit or loss.

Borrowings

Interest-bearing borrowings are initially measured at fair value (with direct transaction costs being amortised over the life of the loan) and are subsequently measured at amortised cost using the effective interest rate method at each reporting date. Interest expenses are recognised in profit or loss.

1.8 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.

1.9 SHARE-BASED PAYMENTS

Share-based payment arrangements in which the Company receives goods or services as consideration for its own equity instruments are accounted for as equity-settled share-based payment transactions. The Company operates a number of equity-settled, share-based compensation plans, under which the Company grants equity shares to employees of subsidiaries and Non-executive Directors.

The fair value of each share option is estimated on the grant date using the Black Scholes option pricing model which utilizes a number of inputs to estimate the fair value of share options such as the current share price, expected term, volatility, interest rate, dividend rate and exercise price.

The fair value of the employee services received in exchange for the grant of the options is recognised as an expense in the subsidiary's profit and loss account, with a corresponding capital contribution from the Company. The expense is recognised in accordance with IFRS2 so that awards with graded vesting are treated as separate grants and the expense associated with each of these separate grants is recognised over the associated vesting period. The amount recognised as an expense is adjusted to reflect the actual number of awards for which the related service and non-market vesting conditions are expected to be met, such that the amount ultimately recognised as an expense is based on the number of awards that do meet the related service and non-market performance conditions at the vesting date. For Performance-based share awards (PSUs) which vest on achievement of specific milestones, known as a non-market performance condition, the associated expense is recognised from the point in time that vesting of the award is considered probable.

1.9 SHARE-BASED PAYMENTS *continued*

The Company records an increase in the cost of investment in its subsidiaries equivalent to the equity-settled share-based payment charge recognised by the subsidiary with the corresponding credit being recognised directly in equity.

The expense associated with equity-based awards to our Non-executive Directors is recognized in the Company's profit and loss account.

2 ACCOUNTING ESTIMATES AND JUDGEMENTS

In preparing the financial statements, management had made judgements and estimates that affect the application of the Company's accounting policies and the reported amounts of assets and liabilities, income and expenses. Although these estimates are based on management's best knowledge of current events and actions, actual results ultimately may differ from those estimates. The estimates and assumptions that have a significant risk of causing a material adjustment to the carrying amounts of assets and liabilities within the next financial year are addressed below:

INVESTMENT IN, AND RECEIVABLE FROM, SUBSIDIARIES

Management performs an annual impairment assessment of the investment held in, and receivable due from, Orchard Therapeutics (Europe) Limited. The receivable is repayable on demand; the expected credit loss associated with the balance is therefore based on the assumption repayment of the loan is demanded at the reporting date, taking into consideration the expected manner of recovery.

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 and intercompany receivable due, management will perform a fair value less cost to sell calculation and then consider whether an impairment of the investment or intercompany receivable is required. Any impairment charge required is recognised in the Company's 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 Company's 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 the year ended 31 December 2022 an impairment of $10.9 million (2021: $299.5 million) and $113.7 million (2021: $121.2 million) have been recognised against the investment in subsidiary and receivable from subsidiary respectively.

Management has performed sensitivity analysis over the inputs to the impairment calculation and concluded that no changes to inputs would result in a material difference to the carrying value of the investment or intercompany receivable that remains post impairments being recognised.

3 INVESTMENT IN SUBSIDIARY UNDERTAKINGS

	$000
Cost	
At 1 January 2022	**299,527**
Share-based payments associated with subsidiary employees	10,929
At 31 December 2022	310,455
Provision for impairment	
At 1 January 2022	**299,527**
Impairment charge for the year	10,929
At 31 December 2022	310,455
Net book value	
At 31 December 2022	**–**
At 1 January 2022	**–**

Share-based payment cost of $10.9 million (2021: $19.9 million) was recorded as a capital contribution from Orchard Therapeutics plc, the Parent Company, to Orchard Therapeutics (Europe) Limited and subsidiaries, as a capital injection into the subsidiary's Balance Sheet.

As the market capitalisation of the Group declined further in 2022, 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 2022, and the Parent Company concluded that the investment was impaired by $10.9 million (2021: $299.5 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.

Details of the Company's subsidiary undertakings as at 31 December 2022 are set out in note 14 in the consolidated group financial statements of Orchard Therapeutics plc.

The Company has provided a parent company guarantee under section 479C of the Companies Act 2006 in respect of all liabilities outstanding at 31 December 2022 of its subsidiary undertaking, Orchard Therapeutics (Europe) Limited (the "Subsidiary"), in order that the Subsidiary may take advantage of the exemption from audit of its individual financial statements for the year ended 31 December 2022.

4 DEBTORS

	2022 $000	2021 $000
Amounts due within one year		
Amounts owed by subsidiary undertakings	**998**	14,957
Other receivables	**183**	937
Deferred financing costs	**462**	693
Prepaid expenses	**26**	3,847
	1,669	20,434

4 DEBTORS *continued*

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 $6.7 million at 31 December 2022 (2021: $6.1 million).

5 SHORT TERM INVESTMENTS

	2022 $000	2021 $000
Current		
Commercial paper	**40,991**	64,406
Corporate bonds	**9,927**	83,590
	50,918	147,996

Investments in commercial paper have fixed coupon rates at 1.1% - 4.9% (2021: 0.1–0.3%) and mature between 1 January 2023 and 31 October 2023 (2021: 1 January 2022 and 30 November 2022). Investments in corporate bonds have fixed coupon rates at 0.4% - 4.5% (2021: 0.2–3.2%) and mature between (2021: 1 January 2022 and 31 October 2023).

6 CREDITORS

	2022 $000	2021 $000
Amounts due within one year		
Bank loans	**9,429**	786
Trade creditors	**616**	308
Accruals	**1,162**	512
	11,207	1,606
Amounts falling due after more than one year		
Bank loans	**22,991**	32,086
	34,198	33,692

7 INTEREST-BEARING LOANS AND BORROWINGS

This note provides information about the contractual terms of the Group's interest-bearing loans and borrowings, which are measured at amortised cost. For more information about the Group's exposure to interest rate and foreign currency risk, see note 24 in the Consolidated financial statements.

	2022 $000	2021 $000
Amounts due within one year		
Bank loans	**9,429**	786
Amounts falling due after more than one year		
Bank loans	**23,236**	32,417
	32,665	33,203
Less: unamortised debt issue costs	**(245)**	(331)
	32,420	**32,872**

7 INTEREST-BEARING LOANS AND BORROWINGS *continued*

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 1 July 2022 and no later than 1 July 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 1 July 2023 and no later than 1 July 2024 upon evidence of the Company having $100 million in cash and cash equivalent investments and attaining a prespecified 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 amortising 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 to the Amended Credit Facility begin amortising 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% of the amount borrowed 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.

7 INTEREST-BEARING LOANS AND BORROWINGS *continued*

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 organisational 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 utilisation of the second term loan and not less than $35.0 million following the utilisation of the third term loan.

In January 2023, the Company again amended and restated the credit facility to change from LIBOR to secured overnight financing rate (SOFR) administered by the Federal Reserve Bank of New York. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

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

8 CAPITAL AND RESERVES

SHARE CAPITAL

	Ordinary shares
In thousands of shares	
In issue at 1 January 2022	125,674
Issued for share options	1,268
Issued as part of a consulting agreement	5
In issue at 31 December 2022 – fully paid	**126,947**

	2022 $000	2021 $000
Ordinary shares allotted and fully paid, £0.10 nominal value	**16,409**	**16,243**

As of 31 December 2022, and 2021, 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 2022, there were 126,947,225 ordinary shares issued and outstanding (2021: 125,674,095). As of 31 December 2022, there were a total of 16,424,167 share options in respect of ordinary shares outstanding (2021: 17,300,740). In addition, as of 31 December 2022 there were 2,063,876 unvested restricted share units outstanding in respect of ordinary shares outstanding (2021: 318,333).

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 2022, the Company. has not declared any dividends (2021: $nil).

8 CAPITAL AND RESERVES *continued*

SHARE PREMIUM

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

SHARE BASED PAYMENTS

The share-based payment reserve arises due to the share options issued by the company to its employees within the Group.

OTHER COMPREHENSIVE INCOME

The Other comprehensive income reserve includes the cumulative net change in the fair value of debt securities measured at fair value through other comprehensive income.

9 RELATED PARTY TRANSACTIONS

Related party transactions are detailed in note 27 in the Company's consolidated financial statements.

The Company has taken advantage of the exemption, under FRS 101 paragraph 8(k) to not 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

Subsequent events are detailed in note 28 in the Company's consolidated financial statements.

12 EMPLOYEES AND DIRECTOR EMOLUMENTS

The monthly average number of people employed by the Company (including Directors) in 2022 was 7 (2021: 7), which is comprised solely of the Directors of the Company.

Amounts paid to Directors consists of:

	2022 $000	2021 $000
Aggregate emoluments	**1,386**	1,333
Aggregate gains made on the exercise of share options	**–**	45
	1,386	**1,378**

Detailed remuneration disclosures are provided in the Directors' Remuneration Report.

13 Explanation of transition to FRS 101

As stated in note 1, these are the Company's first financial statements prepared in accordance with FRS 101. The accounting policies set out in note 1 and 2 have been applied in preparing the financial statements for the year ended 31 December 2022, the comparative information presented in these financial statements for the year ended 31 December 2021 and in the preparation of an opening FRS 101 balance sheet at 1 January 2021 (the Company's date of transition).

In preparing its FRS 101 balance sheet, the Company has adjusted amounts reported previously in financial statements prepared in accordance with its old basis of accounting (FRS 102).

The Company has granted Share Options to employees and directors of the Orchard Therapeutics plc Group with various vesting schedules which are capable of being exercised as they vest in monthly tranches over a period of three to four years from the grant date.

The fair value of the employee services received in exchange for the grant of the options is recognised as an expense in the subsidiary's profit and loss account, with a corresponding capital contribution from the Company. Under FRS 102, the Group measured the awards granted to employees based on the fair value on the date of grant and recognised a compensation expense, in the employing entity's profit and loss account, on a straight-line basis over the vesting period.

Under FRS 101, each tranche is accounted for as a separate share-based payment. Consequently, each instalment would be separately measured and attributed to expense over the related vesting period. The Company has determined and adjusted the fair value, and associated share-based payment expense recognised, for all options with monthly vesting which remain outstanding from the date of transition.

For equity-based awards made to employees of the Group, the expense is recognised by the Company as a capital contribution made to the employing subsidiary and is recorded as an increase in the cost of investment in subsidiaries. For equity-base awards made to Non-executive Directors, the associated expense is recognised in the Company's profit and loss account.

The cumulative impact of this change on the date of transition, being 1 January 2021 was a reduction to cost of investments in subsidiaries, prior to impairment, of $45.1 million, and a corresponding reduction in impairment of investments in subsidiaries of $45.1 million. For the year ended 31 December 2021, the Company has recognised on transition a reduction in additions to investment in subsidiaries of $7.7 million, and a corresponding reduction in impairment charge for the year of $7.7 million.

13 Explanation of transition to FRS 101 *continued*

RECONCILIATION OF PROFIT AND LOSS

	2021 $000
Loss after tax for the year ended 31 December 2021	
As previously reported under FRS 102	(437,351)
Reduction in share-based payment expense	1,164
Reduction in impairment charge in investments in subsidiaries	7,665
Restated under FRS 101	(428,520)

RECONCILIATION OF EQUITY

	FRS 102 2020 $000	Effect of transition to FRS 101 2020 $000	FRS 101 2020 $000	FRS 102 2021 $000	Effect of transition to FRS 101 2021 $000	FRS 101 2021 $000
Equity						
Share capital	12,497	–	12,497	16,243	–	16,243
Share premium	339,435	–	339,435	486,382	–	486,382
Share-based payment reserve	115,062	(47,439)	67,623	143,794	(56,271)	87,523
Other comprehensive income	83	–	83	(137)	–	(137)
Retained earnings	(38,383)	47,439	9,056	(475,735)	56,271	(419,464)
Shareholders' equity	428,694	–	428,694	170,547	–	170,547

There were no transition effects on the previously disclosed values for assets and liabilities.

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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022

OR

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

Commission File Number 001-38722

ORCHARD THERAPEUTICS PLC

(Exact name of Registrant as specified in its Charter)

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

245 Hammersmith Road
London W6 8PW
United Kingdom

(Address of principal executive offices)

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

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

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

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

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

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES ☐ NO ☒

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

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

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

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

If an emerging growth company, indicate by check mark if the Registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

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

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

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

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

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

DOCUMENTS INCORPORATED BY REFERENCE

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

Summary of the Material Risks Associated with Our Business

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

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

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

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains express or implied forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve substantial risks and uncertainties. In some cases, forward-looking statements may be identified by the words "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. The forward-looking statements and opinions contained in this Annual Report are based upon information available to our management as of the date of this Annual Report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. Forward-looking statements contained in this Annual Report include, but are not limited to, statements about:

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

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

You should refer to the section titled “Item 1A. Risk Factors” for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot be assured that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, these statements should not be regarded as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this Annual Report and the documents that we reference in this Annual Report and have filed as exhibits to this Annual Report completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

PART I

Item 1. Business.

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

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

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

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

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

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

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

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

Our *ex vivo* autologous HSC gene therapy approach

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

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

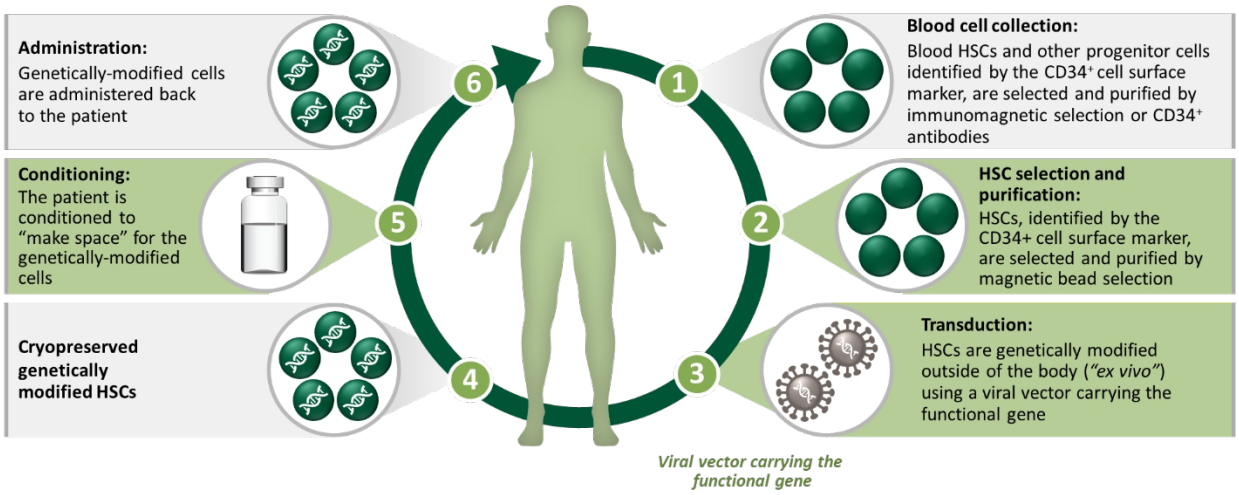
In a pre-clinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America,* or *PNAS*, a sub population of gene-modified HSCs has evidenced the potential to cross the blood-brain barrier, engraft in the brain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

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

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

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

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



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

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

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

Our strategy

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

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

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

Our pipeline

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

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

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

Neurodegenerative Disorders

Gene therapy for treatment of MLD

Disease overview

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

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

Limitations of current therapies

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

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

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

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

Libmeldy approval in Europe as Orphan Drug

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

Data Supporting the Clinical Profile of Libmeldy

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

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

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

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

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

Co-primary endpoints

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

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

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

Key secondary endpoints

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

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

Clinical trial with cryopreserved drug formulation

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

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

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

Data Supporting Safety Profile of Libmeldy

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

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

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

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

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

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

OTL-200 development in the U.S.

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

Gene therapy for treatment of MPS-IH

Disease overview

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

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

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

Limitations of current therapies

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

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

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

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

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

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

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

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

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

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

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

Ongoing clinical trials

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

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

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

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

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

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

Gene therapy for treatment of MPS-IIIA

Disease overviews

MPS-IIIA, also known as Sanfilippo syndrome type A, is a life-threatening metabolic disease that causes accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within the first years after birth, MPS-IIIA and MPS-IIIB patients begin to experience progressive neurodevelopmental delay and decline, including speech delay and eventual loss of language, behavioral disturbances and potentially severe dementia. Ultimately, most patients with MPS-IIIA progress to a vegetative state. Life expectancy for patients with MPS-IIIA is between 10 to 25 years.

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

Limitations of current therapies

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

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

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

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

Proof of concept trial in MPS-IIIA

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

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

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

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

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

Research program in FTD

Disease overview

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

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

Limitations of current therapies

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

Our solution, OTL-204 for treatment of FTD

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

Pre-clinical development of OTL-204

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

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

Immunological Disorders

Research program in NOD2-Crohn's Disease

Disease overview

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

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

Limitations of current therapies

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

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

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

Pre-clinical development of OTL-104

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

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

Other programs

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

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

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

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

Our regulatory strategy

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

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

Manufacturing

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

Global supply network with experienced CDMOs

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

Manufacturing efficiencies and scalability

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

Cryopreservation of our gene therapy programs

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

submissions for marketing approval in the United States and Europe. Our programs in OTL-203 and OTL-201 have already started or will start with cryopreserved formulations. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

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

Commercial operations

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

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

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

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

Intellectual property and barriers to entry

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

We currently rely primarily on know-how and trade secret protection for aspects of our proprietary technologies that we or our licensors believe are not amenable to or appropriate for patent protection, including, for example, clinical data and production information for Libmeldy, Strimvelis and each of our product candidates. Nonetheless, know-how and trade secrets can be difficult to protect. Although we take steps to protect our know-how, trade secrets and other proprietary information, including restricting access to our premises and our confidential information, as well as entering into agreements with our employees, consultants, advisors and potential collaborators, third parties may independently develop the same or

similar know-how, trade secrets or proprietary information or may otherwise gain access to such know-how, trade secrets and other proprietary information or such know-how, trade secrets or other proprietary information may otherwise become known. Moreover, we cannot guarantee that our confidentiality agreements will provide meaningful protection or that they will not be breached, and we may not have an adequate remedy for any such breach. As a result, we may be unable to meaningfully protect our know-how, trade secrets and other proprietary information.

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

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

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment to accommodate for administrative delays caused at the U.S. Patent and Trademark Office, or USPTO, or may be shortened if another patent has a terminal disclaimer with an earlier expiration date. Furthermore, in the United States, the term of a patent covering an FDA-approved drug may be eligible for a patent term extension under the Hatch-Waxman Amendments as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years beyond the expiration of the patent but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. In the future, if we obtain any additional issued U.S. patents covering one of our present or future product candidates, and if such product candidate receives FDA approval, we expect to apply for a patent term extension, if available, to extend the term of the patent covering such approved product candidate. We also expect to seek patent term extensions in any jurisdictions where they are available, but there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such an extension should be granted, and even if granted, they may disagree with our assessment of the appropriate length of such an extension.

License agreements

GSK asset purchase and license agreement

In April 2018, we entered into the GSK Agreement, pursuant to which GSK transferred its portfolio of approved and investigational rare disease gene therapies to us, which included Strimvelis and OTL-200 for MLD, among other programs. GSK also simultaneously novated to us their R&D Agreement with Telethon-OSR.

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

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

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. For example, for Libmeldy, we pay a tiered royalty rate at percentages from the mid-teens to the low twenties. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to OTL-200 may be deferred for a certain

period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048.

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

Telethon-OSR research and development collaboration and license agreement

In April 2018, in connection with our entering into the GSK Agreement, we entered into a deed of novation with GSK, Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, pursuant to which we acquired and assumed all of GSK's rights and obligations under the R&D Agreement with Telethon-OSR for the research, development and commercialization of *ex vivo* HSC gene therapies for certain programs, including OTL-200 and Strimvelis.

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

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

As consideration for the licenses and options granted under the R&D Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are obligated to pay up to an aggregate of €31.0 million in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement, including OTL-200. Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves a certain threshold percentage of the market share.

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

Oxford BioMedica license and development agreement

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

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

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

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

Telethon-OSR license agreement

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

Competition

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

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

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

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

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

- **MPS-I**: The current standard of care for MPS-IH patients is HSCT before the age of 30 months. We are aware that REGENXBIO is developing an AAV-based gene therapy, which is in Phase I trials and to be delivered intracisternally. bluebird bio and Immusoft have both reported that they are developing *ex vivo* cell therapies in the pre-clinical stage. For MPS-I patients that are not suitable candidates for HSCT because they lack a suitable donor, were diagnosed later in life, or have a less severe subtype of MPS-I, the current standard of care for the treatment of MPS-I involves regular intravenous injections of laronidase (Aldurazyme), an ERT commercialized by BioMarin and Sanofi Genzyme. A formulation of laronidase for intrathecal administration is currently under evaluation. JCR Pharmaceuticals is developing an ERT, which is in Phase I trials. Denali Therapeutics has an ERT program in the discovery stage.

- **MPS-IIIA**: There are currently no effective disease modifying treatment options for patients with MPS-IIIA. We are aware of three gene therapy candidates in clinical development. Lysogene is developing an AAV gene therapy product administered through intracerebral injections and regained global commercial rights after its collaboration with Sarepta Therapeutics terminated in July 2022; Abeona Therapeutics has been developing an AAV gene therapy product administered intravenously, which was licensed to Ultragenyx in May 2022 for further clinical development; and Esteve is developing an AAV gene therapy administered through intracerebroventricular injection. Amicus Therapeutics is at the pre-clinical stage of developing an AAV gene therapy for MPS-IIIA. JCR Pharmaceuticals and Denali Therapeutics each have a pre-clinical stage ERT program for MPS-IIIA.

- **GRN-FTD**: There are no approved disease modifying treatments for GRN-FTD. Each of Prevail Therapeutics (now owned by Eli Lilly & Company) and Passage Bio is developing in early-stage clinical trials an AAV gene therapy to be delivered intra-cisterna magna. Alector is developing a monoclonal antibody designed to increase levels of GRN in the brain in late-stage clinical trials, and Denali Therapeutics is developing a modified protein designed to penetrate across the blood-brain barrier at the pre-clinical stage in collaboration with Takeda.

- **NOD2-Crohn's**: There are no approved treatment options specifically for the NOD-2 form of Crohn's disease, and many patients with Crohn's disease have uncontrolled symptoms despite treatment with standard of care, including multiple anti-inflammatory biologics and surgical interventions. We are not aware of any other treatments in development specifically for the NOD-2 form of Crohn's disease.

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

Government regulation

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

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional laws and regulations restricting or prohibiting the processes we may use. Federal and state legislatures, agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive laws and

regulations or interpretations of existing laws or regulations, or claims that our products are unsafe or pose a hazard, could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. biological products development process

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

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

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

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

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

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

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

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

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

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

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

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

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic

indication, particularly for long-term safety follow-up. The FDA generally recommends that sponsors of human gene therapy products integrating vectors such as gammaretroviral and lentiviral vectors and transposon elements observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

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

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

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

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

U.S. review and approval processes

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

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

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

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

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

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

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

Orphan drug designation

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

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

Rare Pediatric Disease Designation and Priority Review Vouchers

Under the FD&C Act, the FDA incentivizes the development of drugs and biological products that meet the definition of a "rare pediatric disease," defined to mean a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making in the United States a drug or biological product for such disease or condition will be received from sales in the United States of such drug or biological product. The sponsor of a product candidate for a rare pediatric disease may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug or biological product application after the date of approval of the rare pediatric disease drug or biological product, referred to as a priority review voucher, or PRV. A sponsor may request rare pediatric disease designation from the FDA prior to the submission of its BLA. A rare pediatric disease designation does not guarantee that a sponsor will receive a PRV upon approval of its BLA. Moreover, a sponsor who chooses not to submit a rare pediatric disease designation request may nonetheless receive a PRV upon approval of their marketing application if they request such a voucher in their original marketing application and meet all of the eligibility criteria. If a PRV is received, it may be sold or transferred an unlimited number of times. Congress has extended the PRV program through September 30, 2024, with the potential for PRVs to be granted through September 30, 2026.

Expedited development and review programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may help expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the

combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

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

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

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on an intermediate clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA is permitted to require, as appropriate, that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of accelerated approval was granted. FDORA also requires sponsors to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. FDORA also gives the FDA increased authority to withdraw approval of a drug or biologic granted accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit. Under FDORA, the FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress. In addition, for products being considered for accelerated approval, the FDA generally requires, unless otherwise informed by the agency, that all advertising and promotional materials intended for dissemination or publication within 120 days of marketing approval be submitted to the agency for review during the pre-approval review period.

RMAT designation

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

Post-approval requirements

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

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

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

U.S. patent term restoration and marketing exclusivity

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

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

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

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

Additional regulation

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

U.S. Foreign Corrupt Practices Act

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

Government regulation outside of the United States

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

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

Clinical trials regulation

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

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

Drug review and approval

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

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

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

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

Data and marketing exclusivity

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

Orphan designation and exclusivity

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

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

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

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

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

Pediatric development

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

PRIME Designation

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

Post-approval controls

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

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

The aforementioned EU rules are generally applicable in the EEA.

Brexit and the Regulatory Framework in the UK

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

Other healthcare laws and compliance requirements

In the United States, our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs may have to comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy and security provisions of the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, and similar state laws, each as amended, as applicable:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;
- the federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payers if they are deemed to "cause" the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a "whistle blower" to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

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

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

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

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

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

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

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

Healthcare reform

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

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

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

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

Coverage and reimbursement

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

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

In addition, coverage and reimbursement for products can differ significantly from payor to payor. One payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree.

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

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

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

Employees and Human Capital Resources

As of December 31, 2022, we had 166 full-time employees. We have no collective bargaining agreements with our employees, and we have not experienced any work stoppages. We consider our relationship with our employees to be positive. We monitor employee engagement through an annual survey and develop a prioritized action plan on an annual basis to address any areas in need of attention. Our human capital objectives include, as applicable, identifying, recruiting, developing, retaining, and incentivizing our existing and prospective employees, as well as optimizing the overall employee experience. The principal purposes of our incentive plans are to attract, retain and motivate our employees. The granting of share-based compensation awards is designed to reward selected employees for long-term shareholder value creation and our cash-based performance bonus awards reward the achievement of annual performance goals. The health and safety of our employees, customers and communities are of primary concern. During the COVID-19 pandemic, we have taken significant steps to protect our workforce, including, but not limited to, implementing a hybrid work model and social distancing protocols consistent with guidelines issued by federal, state and local laws.

Corporate Information

We were originally incorporated under the laws of England and Wales in August 2018 as Orchard Rx Limited (now known as Orchard Therapeutics plc) to become a holding company for Orchard Therapeutics (Europe) Limited (previously known as Orchard Therapeutics Limited). Orchard Rx Limited subsequently re-registered as a public limited company and its name was changed from Orchard Rx Limited to Orchard Therapeutics plc in October 2018. Orchard Therapeutics (Europe) Limited was originally incorporated under the laws of England and Wales in September 2015 as Newincco 1387 Limited and subsequently changed its name to Orchard Therapeutics Limited in November 2015 and to Orchard Therapeutics (Europe) Limited in October 2018. Our registered office is located at 245 Hammersmith Road, London W6 8PW, United Kingdom, and our telephone number is +44 (0) 203 808 8286. Our website address is www.orchard-tx.com. We do not incorporate the information on or accessible through our website into this Annual Report, and you should not consider any information on, or that can be accessed through, our website as part of this Annual Report. We make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file or furnish such materials to the U.S. Securities and Exchange Commission.

Item 1A. Risk Factors.

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

Risks related to our financial position and need for additional capital

We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred net losses. We incurred net losses of $150.7 million and $144.6 million for the twelve months ended December 31, 2022 and 2021, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares, through sales of our ADSs in our initial public offering and follow-on offering, and through private placements of our ordinary shares. We have devoted substantially all of our efforts to research and development, including clinical and pre-clinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Libmeldy in the European Union, building a global commercial infrastructure to support commercialization of Libmeldy (OTL-200) and our product candidates if such product candidates are approved, as well as to building our team. Absent the realization of sufficient revenue from product sales of Libmeldy and from sales of our current or future product candidates, if approved, we may never attain profitability.

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

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

- comply with our obligations as a public company.

Since receiving marketing authorization, only a limited number of patients have been treated with Libmeldy. There is no assurance that revenue from sales of Libmeldy alone will be sufficient for us to become profitable. To become and remain profitable, we must develop and eventually commercialize product candidates with greater market potential. This will require us to be successful in a range of challenging activities, and our expenses will increase as we seek to complete necessary pre-clinical studies and clinical trials of our product candidates, and manufacture, market and sell Libmeldy or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenue that is significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

We have only generated limited sales revenue to date, and we may never be profitable.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully develop and commercialize products. Although we have generated revenue from the sale of Libmeldy and Strimvelis in Europe, we will not achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. Our ability to generate future revenue from product sales depends heavily on our and or our collaborators' success in:

- completing research and pre-clinical development of our product candidates and identifying attractive new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates, including maintaining or reaching target enrollment levels and collecting the necessary follow-up data;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- successfully commercializing Libmeldy in Europe and other product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related post-marketing commitments for regulatory compliance for Libmeldy and Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Libmeldy and Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Libmeldy and Strimvelis, if sales are resumed, and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Libmeldy and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- the impact of geopolitical instability and the ongoing COVID-19 pandemic, including the emergence of new variants;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and manufacturing capabilities;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

We expect that we will continue to incur significant costs associated with commercializing Libmeldy in Europe and any other products for which we obtain marketing approval. Our expenses could increase beyond expectations if the FDA, the EMA or

other regulatory authorities require us to perform clinical or other studies in addition to those that we currently anticipate or if we encounter delays or clinical holds in the development of our product candidates. Even if we generate more significant revenue from sales of Libmeldy in Europe and generate revenue from the sale of any other approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We may not receive any additional amounts under the Securities Purchase Agreement, dated March 6, 2023.

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

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

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

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

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

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

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

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

needed or on reasonable terms, or at all, we would be forced to delay, reduce or eliminate certain of our ongoing activities, such as research and development programs and commercialization efforts.

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

- the success of our commercialization efforts and market acceptance of Libmeldy in Europe;
- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities to support Libmeldy in Europe and any other products for which we obtain marketing approval, including costs relating to quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors on a timely basis for Libmeldy and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related post-marketing commitments for regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, pre-clinical development and clinical trials for our product candidates or future product candidates, including the need to conduct long-term follow-up for up to 15 years for our development programs and additional clinical trials to support marketing approvals for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Libmeldy and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

Identifying potential product candidates and conducting pre-clinical testing and clinical trials, as well as preparing for the potential commercialization of these product candidates, is a time-consuming, expensive and uncertain process that takes years to complete. We may never generate the necessary data or results required to obtain marketing approval and achieve product sales for any products other than Libmeldy and Strimvelis. In addition, Libmeldy and any other products for which we obtain and maintain marketing approval may not achieve commercial success. Any product revenue from our product candidates, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

We may seek to raise capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise capital through the sale of equity, convertible debt securities or other equity-based derivative securities, ownership percentages of all our shareholders may be diluted and the terms may include liquidation or other preferences that adversely affect their rights as shareholders. Any additional indebtedness we incur would result in additional increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our ADSs to decline and existing shareholders may not agree with our financing plans or the terms of such financings. If we raise funds through strategic partnerships, alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, or our product candidates, or grant licenses on terms unfavorable

to us. Adequate financing may not be available to us on acceptable terms, or at all. In the past several years, global credit and financial markets have experienced volatility, instability and disruptions, including as a result of the COVID-19 pandemic, geopolitical instability and other macroeconomic factors. The significant volatility in public equity markets and the disruptions to the U.S. and global economies may make it more difficult to raise capital through sales of our ADSs on favorable terms, or at all.

Our limited operating history may make it difficult to evaluate the success of our business to date and to assess our future viability.

We were incorporated in August 2018 to become a holding company for Orchard Therapeutics (Europe) Limited, which was founded in 2015, and its subsidiaries. Our operations to date have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring certain of our product candidate portfolios and rights to our technology, identifying potential product candidates, undertaking pre-clinical studies and planning and supporting clinical trials of our product candidates, establishing research and development and manufacturing capabilities, establishing a quality management system, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union and building a global commercial infrastructure to support commercialization of Libmeldy. Consequently, any predictions about our future success or viability may not be as accurate as they might be if we had a longer operating history. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and setbacks.

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

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

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

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

Risks related to the discovery, development and regulatory approval of our product candidates

Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our autologous *ex vivo* gene therapy approach, and our future success depends on our successful development of commercially viable gene therapy products. There can be no assurance that we will not experience problems or delays in developing new products and that such problems or delays will not cause unanticipated costs or that any such development problems can be solved. Although we have established a commercial infrastructure for the production of Strimvelis in the European Union and we are building a global commercial infrastructure to support commercialization of Libmeldy, we may experience delays in establishing a sustainable, reproducible and scalable manufacturing capability with commercial CDMO partners, which may prevent us from commercializing our product candidates for which we obtain marketing approval on a timely or profitable basis, if at all.

In addition, the clinical trial requirements of the FDA, EMA and other foreign regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate can vary substantially, for example, based upon the

type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than the process for other, better known or more extensively studied product candidates. To date, only a limited number of gene therapies have received marketing authorization from the FDA or EMA. We have limited experience in preparing, submitting and maintaining regulatory submissions. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, Europe or in other jurisdictions, or how long it will take to commercialize Libmeldy in Europe or any other product candidates for which we obtain marketing approval. Approvals by the EMA may not be indicative of what the FDA may require for approval, and vice versa.

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

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

Due to the nature of the indications our product candidates are designed to treat, and the limited number of patients with these conditions, a placebo-controlled and blinded study is not always practicable for ethical and other reasons. Accordingly, in some cases our registrational programs rely on natural history models to demonstrate clinical efficacy. While the FDA recognizes the potential for natural history models to alleviate the need for placebo arms in trials for drugs that target very rare diseases, where trial recruitment can be especially challenging, the FDA has found the use of natural history data as a historical comparator to be unsuitable for adequate and well-controlled trials in many circumstances. The FDA generally finds trials using historical controls to be credible only when the observed effect is large in comparison to variability in disease course. It is possible the FDA will not consider our comparisons to natural history data and, where available, historical transplant data or intra-subject comparison between before gene therapy and after gene therapy, to provide clinically meaningful results. Additionally, even though OTL-200 for MLD has achieved the primary endpoints in its ongoing registrational clinical trial, the FDA has not yet approved the clinical meaningfulness of the trial results and their sufficiency to support a marketing authorization.

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

It is possible that the FDA or EMA may recommend or require us to conduct further studies, analyses or registrational trials with respect to our product candidates, possibly involving a larger sample size or a different clinical trial design. The FDA or EMA may also require that we conduct a longer follow-up period of patients treated with our product candidates prior to accepting a BLA or MAA submission, as applicable.

In addition, data obtained from pre-clinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other foreign regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. The FDA may further refer any future BLA submission to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. This review may add to the time for approval, and although the FDA is not bound by the recommendation of an advisory committee, objections or concerns expressed by the advisory committee may cause the FDA to delay or deny approval. We also may experience regulatory delays or rejections as a result of many factors, including serious adverse events, or SAEs, involving our product candidates, changes in regulatory policy or changes in requirements

during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

We expect that the FDA and EMA will assess the totality of the safety and efficacy data from our product candidates in reviewing any future BLA or MAA submissions. Based on this assessment, the FDA or EMA may require that we conduct additional pre-clinical studies or clinical trials prior to submitting or approving a BLA or MAA for our target indications. It is possible that the FDA or EMA may not consider the results of our clinical trials, including reliance on foreign clinical data, to be sufficient for approval of our product candidates. If the FDA or EMA require additional trials, we would incur increased costs and delays in the marketing approval process, which may require us to expend more resources than we have available. In addition, it is possible that the FDA and EMA may have divergent opinions on the elements necessary for a successful BLA and MAA submission, respectively, which may cause us to alter our development, regulatory or commercialization strategies.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. Such requirements may lengthen the regulatory review process, require us to perform additional studies, and increase our development costs or may force us to delay, limit or terminate certain of our programs.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. The FDA has established the Office of Therapeutic Products within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review when called upon. The NIH has refocused the NIH Recombinant DNA Advisory Committee and changed its name to the Novel and Exceptional Technology and Research Advisory Committee, or NExTRAC. NExTRAC is a federal advisory committee that provides recommendations to the NIH Director and a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies, which include, but are not restricted to, technologies surrounding advances in recombinant or synthetic nucleic acid research such as human gene transfer. These regulatory review committees and advisory groups and any new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions.

The FDA and EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. Adverse events in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates, which could require additional pre-clinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval. Similarly, the European Commission may issue new guidelines concerning the development and marketing authorization for gene therapies and require that we comply with these new guidelines, which could require additional pre-clinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval.

As we advance our product candidates, we are required to consult with these regulatory and advisory groups and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects might be materially and adversely affected.

The FDA and EMA have released a series of final guidance documents and a draft guidance document for consultation, which among other topics, included various aspects of gene therapy product development, review and approval, including aspects relating to clinical and manufacturing issues related to gene therapy products. We cannot be certain whether future guidance will be issued and be relevant to, or have an impact on, our gene therapy programs or the duration or expense of any applicable regulatory development and review processes.

Libmeldy, Strimvelis and our product candidates and the process for administering Libmeldy, Strimvelis and our product candidates may cause serious or undesirable side effects or adverse events or have other properties that could delay or prevent regulatory approval, limit commercial potential or result in significant negative consequences for our company.

Following treatment with our gene therapies, patients may experience changes in their health, including illnesses, injuries, discomforts or a fatal outcome. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of our product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in previous clinical trials, as well as conditions that did not occur or went undetected in previous clinical trials, will be reported by patients. Gene therapies are also subject to the potential risk that occurrence of adverse events will be delayed following administration of the gene therapy due to persistent biological activity of the genetic material or other components of the vectors used to carry the genetic material. Many times, additional safety risks, contraindications, drug interactions, adverse events and side effects are only detectable after investigational products are tested in larger scale registrational trials or, in some cases, after they are made available to patients on a commercial scale after approval. The FDA generally requires long-term follow-up of study subjects. Although the risk profile of a gene therapy candidate is a factor in determining the adequacy of such long-term follow-up, the FDA currently recommends that sponsors observe study subjects for potential gene therapy-related adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects. If additional experience indicates that any of our product candidates -- or similar products developed by other companies -- have side effects or causes serious or life-threatening side effects, the development of such product candidate may fail or be delayed, or, if the product has received regulatory approval, such approval may be revoked or limited.

Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. Possible adverse side effects and adverse events that may occur with treatment with gene therapy products include an immunologic reaction early after administration that could substantially limit the effectiveness of the treatment or represent safety risks for patients. Another traditional safety concern for gene therapies using viral vectors has been the possibility of insertional mutagenesis (or oncogenesis) by the vectors, leading to malignant transformation of transduced cells. There have been several adverse events and SAEs attributed to gene therapy treatments in the past, including reported cases of leukemia with the use of gammaretrovirus vector and death seen in other clinical trials. In October 2020, we were notified that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with lymphoid T cell leukemia. Subsequent findings confirmed that the patient's leukemia was due to insertional oncogenesis attributable to treatment with Strimvelis. The EMA's Committee for Medicinal Products for Human Use, or CHMP, concluded that the risk-benefit balance remains favorable and requested that the Strimvelis product information identify insertional mutagenesis (or oncogenesis) as an "important identified risk" instead of an "important potential risk" in light of this event.

Strimvelis is the only gammaretroviral vector-based gene therapy in our portfolio. Libmeldy and all of our pipeline therapies employ the self-inactivating (SIN) lentiviral vector-based approach, which has been specifically designed to avoid insertional oncogenesis after administration. Although to our knowledge and as of the date of this report no evidence of insertional oncogenesis has been observed with lentiviral vector-based HSC gene therapy in any of our programs, there can be no assurance that this will continue to be the case. Moreover, while our gene therapy approach is designed to avoid immunogenicity after administration, there can be no assurance that patients would not develop antibodies that may impair treatment. Our approach involves the use of integrating vectors, which have the potential for genomic disruption and therefore could interfere with other genes with adverse clinical effects. If any of our gene therapy product candidates demonstrates adverse side effects or adverse events at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

In addition to side effects and adverse events caused by our product candidates, the conditioning, administration process or related procedures also can cause adverse side effects and adverse events. A gene therapy patient is generally administered cytotoxic drugs to remove stem cells from the bone marrow to create sufficient space in the bone marrow for the modified stem cells to engraft and produce new cells. This procedure compromises the patient's immune system. While certain of our product candidates are designed to utilize milder conditioning regimens that are intended to require only limited removal of a patient's bone marrow cells, the conditioning regimens may not be successful or may nevertheless result in adverse side effects and adverse events. If in the future we are unable to demonstrate that such adverse events were caused by the conditioning regimens used, or administration process or related procedure, the FDA, the European Commission, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all target indications. Even if we are able to demonstrate that adverse events are not related to the drug product or the administration of such drug product, such occurrences could affect patient recruitment, the ability of enrolled patients to complete the clinical trial, or the commercial viability of any product candidates that obtain regulatory approval.

Additionally, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval to ensure that the benefits of our product candidates outweigh their risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, and restrictions on how or where the product can be distributed, dispensed or used. Other non-U.S. regulatory

authorities could impose other specific obligations, such as through a risk management plan, or RMP, submitted to the EMA. Furthermore, if we or others later identify undesirable side effects caused by Strimvelis, Libmeldy or our product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product or product candidate;
- regulatory authorities may require additional warnings or limitations of use in product labeling;
- we may be required to change the way a product candidate is distributed, dispensed, or administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of Libmeldy and any other products for which we obtain marketing approval and could significantly harm our business, prospects, financial condition and results of operations.

To date, most of the clinical trials for our product candidates were conducted as investigator-sponsored clinical trials using drug product manufactured at academic sites. Regulatory authorities may closely scrutinize the data collected from these trials and may require that we conduct additional clinical trials prior to any marketing approval.

We have limited experience conducting company-sponsored clinical trials and to date most of our product candidates have been evaluated under investigator-sponsored clinical trials using drug product manufactured at the applicable or relevant academic site. We did not control the design or administration of these investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these clinical trials. Investigator-sponsored clinical trials are often conducted under less rigorous clinical and manufacturing standards than those used in company-sponsored clinical trials. For example, the drug product used in our company-sponsored clinical trials is manufactured by third party CDMOs using current good manufacturing practices, or cGMP, standards. Accordingly, regulatory authorities may closely scrutinize the data collected from these investigator-sponsored clinical trials and may require us to obtain and submit additional clinical data prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates. We will be required to demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CDMOs, and we cannot provide assurances that we will satisfy such comparability requirements. We may also be required to demonstrate improved quality and drug product manufacturing state of control in accordance with cGMP standards.

For example, in the compassionate use program conducted by Great Osmond Street Hospital, or GOSH, one patient experienced an SAE, staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. A similar SAE, bacteremia, was observed in the clinical trial conducted at University of California Los Angeles, or UCLA, for our since-returned program OTL-101 for ADA-SCID with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. The bacteremia resolved on day three without sequelae. We believe that our commercial manufacturing processes for our product candidates, together with cryopreserved formulation, which allows for safety/microbiological testing to be completed prior to drug infusion to the patient, could mitigate the risk of contamination of products that might have resulted in such infections, but there can be no assurance that this will be the case. To the extent that the results of our current company-sponsored trials are inconsistent with, or different from, the results of any investigator-sponsored trials or raise concerns regarding our product candidates, the regulatory authorities may question the results from some or all of these trials, and may require us to obtain and submit additional clinical data from drug product manufactured by CDMOs prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates.

We may be unable to demonstrate comparability between (i) drug product manufactured using HSCs derived from a patient's mobilized peripheral blood and drug product manufactured using HSCs derived from a patient's bone marrow, (ii) drug product that has been cryopreserved and fresh drug product, and (iii) the manufacturing process used at academic centers with the manufacturing process used at CDMOs. Failure to demonstrate such comparability could affect our ability to secure regulatory approval for our product candidates or could affect the commercial viability of our product candidates if approved for use using only HSCs derived from bone marrow or using only fresh drug product.

To date, most of the patients who have been treated in clinical trials involving our product candidates received fresh drug product manufactured using HSCs derived from the patient's bone marrow at academic centers. We are currently evaluating our product candidates and plan to seek marketing approval using drug product that is manufactured at CDMOs using HSCs derived from either the patient's bone marrow or mobilized peripheral blood and using a procedure by which the gene-

modified HSCs are cryopreserved in order to maintain the cellular material in suitable condition until it is thawed prior to being infused into the patient.

In those cases where clinical trials were conducted using vector or drug product manufactured at academic research centers, we will need to demonstrate comparability between vector and drug product manufactured by our CDMOs with vector or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another. In other cases, we may elect to initially seek approval of our product candidate using one cellular source only and subsequently seek approval for the use of the other cellular source. We cannot be assured that the FDA, EMA or other regulatory authority will not require us to conduct additional analytical studies (including comparability analyses), pre-clinical studies or clinical trials before approving our product candidates using these intended commercial production methods and processes. Moreover, we cannot be assured that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval of our product candidates using these production methods and processes.

If any of the FDA, EMA or other regulatory authority does not accept our comparability data or if an adequate potency assay for a product candidate is not available or supported by such regulatory authority, our regulatory approval for such product candidate, if any, will be limited or delayed. For example, if one or more of these regulatory authorities does not accept that our cryopreservation process produces a product candidate that is comparable to our fresh drug product, our regulatory approval, if any, would be limited to our fresh product candidate until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials or require additional test method development. Potency assays that measure strength (e.g., enzymatic activity, or other relevant function) of each active ingredient are required for release testing of licensed biological drug products, comparability and stability analysis.

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

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

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

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

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

If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as bone marrow transplantation or enzyme replacement therapy. We may never succeed in demonstrating efficacy and safety of our product candidates or any future product candidates in clinical trials or in obtaining marketing approval thereafter.

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

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

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

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

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

For example, although sustained clinical activity has been observed in clinical trials to date for Libmeldy (OTL-200), follow-up in these clinical trials is ongoing and there can be no assurance that the results, in each case as of the applicable primary endpoint measurement date, seen in clinical trials of any of our product candidates ultimately will result in success in clinical trials or provide adequate support for marketing approvals by the FDA, in the case of Libmeldy, without conducting further clinical trials. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical trials, and may not be repeated or observed in ongoing or future trials involving our product candidates. There are limited data concerning long-term safety and efficacy following treatment with our product candidates. Our product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in pre-clinical studies. Our product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical trials. There can be no assurance that any of these trials will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates. In addition, there can be no assurance that we will be able to achieve the same or similar success in our pre-clinical studies and clinical trials of our other product candidates.

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

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

assured that the results observed in these cases will be observed in our ongoing or future clinical trials or that our ongoing and future clinical trials will ultimately be successful.

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

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

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields generally, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. Additionally, the COVID-19 global pandemic has had and may continue to have a sustained impact on our ability to recruit and follow-up with patients either due to continued or renewed restrictions on travel or shelter-in-place orders or policies or due to changes in patient willingness to participate in trials or travel to study sites in the wake of the pandemic. Additionally, COVID-19 related study site policies may create delays or setbacks in our ability to continue to enroll or to dose patients. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

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

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- safety profile, to date, of the product candidate under study;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases, including any required pre-treatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- degree of progression of the subject's disease at the time of enrollment;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective subjects;
- the impact of the COVID-19 global pandemic or future pandemics or similar events on patients' willingness and ability to participate in clinical trials or on study site policies;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor subjects adequately during and after treatment.

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

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

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

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

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

- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable patients and in sufficient volume to participate in our clinical trials;
- imposition of a clinical hold by regulatory agencies;
- failure by our academic partners, CROs, other third parties or us to adhere to clinical trial protocol and record keeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- delays in patient enrollment, missed assessments resulting from remote follow-up visits, or delays in completion of participation as a result of the impact of the COVID-19 global pandemic or future pandemics or similar events;
- the occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete pre-clinical and clinical development could result in additional costs to us or impair our ability to generate revenue. In addition, if we make changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. Clinical trial delays could also shorten any periods during which we may

have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

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

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

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

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

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

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

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

Even if we complete the necessary pre-clinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or any future collaborators are not able to obtain, or if there are delays in obtaining,

required regulatory approvals, we or they will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

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

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

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

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

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

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by the EMA or other regulatory authorities in other countries or jurisdictions, and approval by the EMA or another regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. For example, though we received standard marketing authorization of Libmeldy (OTL-200) from the European Commission in December 2020, there is no guarantee that we will receive approval from the FDA.

Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional pre-clinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit an MAA to the EMA for approval of our product candidates in the European Union, but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process.

Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements

could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

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

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

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

To date, most of the clinical trials conducted on our product candidates have been conducted outside the United States. Although the FDA may accept data from clinical trials conducted outside the U.S., acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept data from any trial that we conduct outside the U.S., due to study design or otherwise, it would likely result in the need for additional trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates. Further, if we do not have an IND open for a product candidate, we forego more frequent interactions and dialogue with the FDA regarding the design and conduct of our trials as well as product comparability, which may delay or halt the development of such product candidates later in development should the FDA later disagree with the design or conduct of our trials or product comparability approach.

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

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

The FDA and comparable other regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. OTL-200 for MLD received RMAT designation from the FDA, and OTL-203 for MPS-IH received a Priority Medicines, or PRIME, designation from EMA. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review process, they generally do not change the

standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

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

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

In addition, the FDA has granted Rare Pediatric Disease designation to OTL-200 for MLD, OTL-201 for MPS-IIIA and OTL-203 for MPS-IH, and we may seek Rare Pediatric Disease designation for some of our other product candidates. The FDA defines a “rare pediatric disease” as a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making in the U.S. a drug for such disease or condition will be received from sales in the U.S. of such drug. Under the FDA’s Rare Pediatric Disease Priority Review Voucher, or PRV, program, upon the approval of a BLA for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for a Rare Pediatric Disease PRV that can be used to obtain priority review for a subsequent new drug application or BLA. The PRV may be sold or transferred an unlimited number of times. Congress has extended the PRV program through September 30, 2024, with potential for PRVs to be granted through September 30, 2026. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for Libmeldy (OTL-200), OTL-201 for MPS-IIIA and OTL-203 for MPS-IH and qualify for such a PRV, the program may no longer be in effect at the time or the value of any such PRV may decrease such that we are may not be able to realize the benefits of such PRV.

In addition, we may seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, there can be no

assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA approval. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

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

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

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

We have sought and received orphan drug designation for Libmeldy (OTL-200) and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-203 for MPS-IH from the FDA, but we may be unable to obtain orphan drug designation for our other product candidates. Even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan designation in respect of a medicinal product if the sponsor can establish that such product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EU. Additionally, orphan designation may be granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely such products would generate sufficient return in the EU to justify the necessary investment their development. In either case, the applicant for orphan designation must also demonstrate that no satisfactory method of diagnosis, prevention, or treatment for the condition has been authorized for marketing in the EU (or, if a method exists, the new product would be a significant benefit to those affected by the condition).

We have sought and received orphan drug designation for Libmeldy and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-203 for MPS-IH from the FDA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our other product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not mean that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or EMA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the EU. The exclusivity period in the EU can be reduced to six years if a product no longer meets the criteria for orphan designation, including if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity

may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

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

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

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

As part of its marketing authorization process, the EMA may grant marketing authorizations for certain categories of medicinal products on the basis of less complete data than is normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required or in the interests of public health. In such cases, it is possible for the CHMP to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating or life-threatening diseases and those designated as orphan medicinal products.

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

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

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

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

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

Libmeldy and any of our product candidates for which we obtain regulatory approval will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. For example, as a post-marketing commitment, we are continuing to follow patients in the OTL-200 clinical development program for up to 15 years, and data will be presented to regulators at agreed points in order to further characterize the long-term efficacy and safety of Libmeldy.

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

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

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

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

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

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

In addition, the FDA's policies, and those of the EMA and other regulatory authorities, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we

may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

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

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

Risks related to manufacturing and supply

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience, and we rely on third party manufacturers that are often our single source of supply. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial products or our product candidates or otherwise harm our business.

Biological products are inherently difficult to manufacture, and gene therapy products are complex biological products, the development and manufacture of which necessitates substantial expertise and capital investment. Libmeldy, Strimvelis and our product candidates are individually manufactured for each patient using complex processes in specialized facilities. Our production process requires a variety of raw materials, some of which are highly specialized, including the viral vector that encodes for the functional copy of the missing or faulty gene to treat a specific disease. Some of these raw materials have limited and, in some cases, sole suppliers. Even though we plan to have back-up supplies of raw materials whenever possible, we cannot be certain such supplies will be sufficient if our primary sources are unavailable. A shortage of a critical raw material or a technical issue during manufacturing may lead to delays in clinical development or commercialization of our product candidates. Additionally, each manufacturing batch must meet certain analytical specifications to be released and production difficulties caused by unforeseen events may delay the availability of one or more of the necessary raw materials or delay the manufacture of our product candidates for use in clinical trials or for commercial supply.

We have contracted with third party CDMOs for the manufacture of our viral vectors and drug product. We expect these CDMOs will be capable of providing sufficient quantities of our viral vectors and gene therapy products to meet the anticipated scale of our clinical trials and current and initial commercial demands, if any additional products are approved. However, to meet our projected needs for further commercial manufacturing and clinical trials of new product candidates, third parties with whom we currently work might need to increase their scale and frequency of production or we will need to secure alternate suppliers or develop in-house capabilities. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements; however, identifying and establishing relationships with such sources, if necessary, could result in significant delays or material additional costs, which could delay or prevent the development of our product candidates and would have a negative impact on our business, financial condition and results of operations.

Additionally, the manufacturers of pharmaceutical products must comply with strictly enforced cGMP requirements, state and federal regulations, as well as foreign requirements when applicable. Any failure of our CDMOs to adhere to or document compliance to such regulatory requirements could lead to a delay or interruption in the availability of our program materials for clinical trials. If our manufacturers were to fail to comply with the FDA, EMA, or other regulatory authority, it could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension

or withdrawal of approvals, license revocation, seizures or recalls of raw materials, product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. Our dependence upon others for the manufacture of our gene therapies may also adversely affect our future profit margins and our ability to commercialize any product candidates that receive regulatory approval on a timely and competitive basis.

Delays in obtaining regulatory approval of our or our CDMOs' manufacturing process and facility or disruptions in our manufacturing process may delay or disrupt our commercialization efforts. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product.

Before we can begin to commercially manufacture our viral vector or product candidates in a CDMO facility, we must obtain regulatory approval from the FDA for our manufacturing processes and for the facility in which manufacturing is performed. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product; therefore, the time frame required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our CDMOs manufacturing facility by the FDA and other relevant regulatory authorities before any of our gene therapy product candidates can obtain marketing approval.

In order to obtain approval, we will need to ensure that all of our processes, quality systems, methods, equipment, policies and procedures are compliant with cGMP, and perform extensive audits of vendors, contract laboratories, CDMOs and suppliers. If any of our vendors, contract laboratories, CDMOs or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to spend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs.

We do not have experience as a company managing a complex supply chain or satisfying manufacturing-related regulatory requirements.

The FDA, EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, EMA or other foreign regulatory authorities may require that we not distribute a product lot until the relevant agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in a viral vector or a gene therapy product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects. Problems in our manufacturing processes could restrict our ability to meet market demand for our products.

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

Once collected from the patient, the cellular source material must be prepared and stored according to specified procedures. While we intend to standardize the processes at treatment centers, if there is a deviation of the processes, the cellular source material from a patient could be adversely impacted and potentially result in manufacturing failures. The patient's cellular materials must be transported to the manufacturing facility using a shipping container that maintains the material at a cool temperature and must typically be delivered and processed within three days of collection. While we intend to use reputable couriers and agents for the transport of such materials, if the shipping container is opened or damaged such that the cool temperature is not maintained, the cellular source material may be adversely impacted and it may not be feasible to manufacture a drug product for the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, being held up at a customs point, COVID-19 impacts or other events, the cellular source material may not be delivered within a time window that will allow for its use for the successful manufacture of a drug product.

Similarly, the patient's autologous drug product must be returned to the clinical site for administration into the patient using a specialized shipping container that maintains the material at a very low temperature for a period of typically up to ten days. While we intend to use reputable couriers and agents for the transport of our drug products, if the shipping container is opened or damaged such that the very low temperature is not maintained, the drug product may be adversely impacted and it may not be feasible to administer it to the patient or, if administered, it could cause harm to the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, being held up at a customs point, COVID-19 impacts or other events, and is not delivered to the clinical site within the time period that the very low temperature is maintained, the drug product may be adversely affected and be unable to be administered or, if administered, could cause harm to the patient.

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

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

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

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

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

Given the nature of biologics manufacturing, there is a risk of microbial contamination. Any microbial contamination could adversely affect our ability to produce, release or administer our gene therapies on schedule and could, therefore, harm our results of operations and cause reputational damage. Additionally, although our gene therapies are tested for microbial contamination prior to release, if a contaminated product was administered to a patient, it could result in harm to the patient. Some of the raw materials required in our manufacturing processes are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our vectors or drug product could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our development timelines and our business.

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

Our viral vectors and drug products are manufactured using technically complex processes in specialized facilities, sometimes using specialized equipment with highly specific raw materials and other production constraints. The complexity of these processes, as well as strict government standards for the manufacture and storage of our gene therapies, subjects us to manufacturing risks. While viral vectors and drug product released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following their release. In addition, process deviations or unanticipated effects of approved process changes may result in viral vector or drug product not complying with stability requirements or specifications. Our viral vectors and drug product must be stored and transported at temperatures within a certain range. If these environmental conditions deviate, our viral vectors and drug products' remaining shelf-lives could be impaired or their efficacy and safety could be negatively impacted, making them no longer suitable for use. For example, patients' cellular material must be received by the manufacturing facility typically within three days after collection, and our gene therapy must be received by the clinical site typically within ten days after shipping from the manufacturing facility. The occurrence, or suspected occurrence, of manufacturing and distribution difficulties can lead to lost inventories and, in some cases, product recalls, with consequential reputational damage and the risk of product liability. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product launches. Any interruption in the supply of finished products, due to transportation or other delays, including delays or disruptions resulting from the impact of the COVID-19 pandemic, or the loss thereof could hinder our ability to timely distribute our products and satisfy customer demand. Any unforeseen failure in the storage of the viral vectors or drug

products or loss in supply could delay our clinical trials and result in a loss of our market share for our commercial products or our product candidates, if approved, and negatively affect our business, financial condition, results of operations and prospects.

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

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

Risks related to our reliance on third parties

We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialize product candidates. These collaborations may not be successful.

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

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

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

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

Any collaborations we enter into in the future may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- we may not achieve any milestones, or receive any payments, under our collaborations, including milestones or payments that we expect to achieve or receive;
- the clinical trials conducted as part of these collaborations may not be successful;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our shareholders about the status of such product candidates;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates developed in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under such collaborations. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected.

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing shareholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process will likely be time-consuming and complex. Our ability to reach a definitive collaboration agreement in such instances will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of several factors. If we license rights to additional product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

We utilize, and expect to continue to utilize, third parties to conduct some or all aspects of our vector production and product manufacturing for the foreseeable future, and these third parties may not perform satisfactorily.

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

trials and for Libmeldy and other products for which we obtain marketing approval, if any, we intend to utilize materials manufactured by CDMOs. If our academic partners or these CDMOs do not successfully carry out their contractual duties, meet expected deadlines or manufacture our viral vector and product candidates in accordance with regulatory requirements or if there are disagreements between us and our academic partners or these CDMOs, we will not be able to complete, or may be delayed in completing, the pre-clinical studies and clinical trials required to support approval of our product candidates or the FDA, EMA or other regulatory agencies may refuse to accept our clinical or pre-clinical data. In such instances, we may need to enter into an appropriate third-party relationship, which may not be readily available or available on acceptable terms. This could cause additional delay or increased expense prior to the approval of our product candidates and could have a negative impact on our business, financial condition, results of operations and prospects.

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

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

In addition to our current CDMOs, we may rely on additional third parties to manufacture our viral vectors or drug products in the future and to perform quality testing. Reliance on these third parties entails risks that we would not be subject to if we manufactured the product candidates ourselves, including:

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

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

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

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our pre-clinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing pre-clinical and clinical programs. While we will have agreements governing the activities of our academic partners and CROs, we will control only certain aspects of their activities and have limited influence over their actual performance.

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

with GLP and GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the EEA, and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. The FDA, EMA or comparable foreign regulatory authorities may deem the clinical data generated in our clinical trials unreliable and may require us to perform additional clinical trials before approving our marketing applications if, among other things, we fail to exercise adequate oversight over any of our academic partners or CROs or if our academic partners or CROs do not successfully carry out their respective contractual duties or obligations, fail to meet expected deadlines or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements. We cannot assure that upon a regulatory inspection of us, our academic partners or our CROs or other third parties performing services in connection with our clinical trials, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under applicable cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

We do not control the design or conduct of the academic-sponsored trials, and it is possible that the FDA or EMA will not view these academic-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. Such arrangements provide us certain information rights with respect to the academic-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the academic-sponsored trials. However, we do not have control over the timing and reporting of the data from academic-sponsored trials, nor do we own the data from the academic-sponsored trials. If we are unable to confirm or replicate the results from the academic-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of OTL-201 for MPS-IIIA, OTL-203 for MPS-IH or any other product candidate investigated in an academic-sponsored clinical trial. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the academic-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or EMA may disagree with the sufficiency of our right of reference to the pre-clinical, manufacturing or clinical data generated by these academic-sponsored trials or our interpretation of pre-clinical, manufacturing or clinical data from these academic-sponsored trials. If so, the FDA or EMA may require us to obtain and submit additional pre-clinical, manufacturing or clinical data.

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

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and drug products. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain, and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing CDMOs for our viral vectors and drug product, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials, including in some cases critical raw materials used in the manufacture thereof, must be manufactured in accordance with cGMP. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our viral vectors or product candidates that may not be detectable in final product testing. We or our CDMOs must supply all necessary documentation in support of a BLA or MAA on a timely basis and must adhere to the FDA's and EMA's cGMP and other applicable regulations that are enforced through facilities inspection programs. Some of our CDMOs have not produced a commercially-approved product and have never been inspected by the FDA or other regulatory body. Our quality systems and the facilities and quality systems of some or all of our CDMOs must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our viral vector or drug product or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted.

If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory

authority may require remedial measures that may be costly or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

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

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

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

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

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

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

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

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

- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers;
- interruptions, shortages, delivery delays and potential discontinuation of supply as a result of the ongoing COVID-19 global pandemic, or any recurrence of the pandemic or future pandemics; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

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

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

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

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

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

Risks related to commercialization of our product candidates

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

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

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

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

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

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

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

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

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

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

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

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

Many of our competitors have significantly greater financial, product candidate development, manufacturing and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for their products, and mergers and acquisitions within these industries may result in even more

resources being concentrated among a smaller number of larger competitors. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our business would be materially and adversely affected if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, have broader market acceptance, are more convenient or are less expensive than any product candidate that we may develop.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

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

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

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

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

- the potential efficacy and potential advantages over alternative treatments;
- the frequency and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the frequency and severity of any side effects resulting from the conditioning regimen or follow-up requirements for the administration of our product candidates;
- the relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

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

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

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

We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, if approved. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a payor not to cover our gene therapies could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition.

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

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

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenue from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. Some countries may also require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control

efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenue we are able to generate from the sale of the product in that particular country. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our product candidates. Historically, products launched in the European Union do not follow price structures of the U.S. and generally prices tend to be significantly lower.

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

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

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

Risks related to our business operations

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology with only a limited number of gene therapy products approved to date. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. Adverse events in other lentiviral gene therapy trials unrelated to our product candidates could negatively impact our business. Our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates (such as the many adverse events that typically arise from the conditioning process), or adverse events in other lentiviral gene therapy trials, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

Increasing demand for compassionate use of our unapproved therapies could result in losses.

We are developing our autologous *ex vivo* gene therapies to address rare diseases for which there are currently limited or no available therapeutic options. Media attention to individual patients' expanded access requests has resulted in the introduction and passage of legislation at the local and national level referred to as "Right to Try" laws, which are intended to help enable patient access to unapproved therapies. Such legislation includes the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, which was signed into law in May 2018. New and emerging legislation regarding expanded access to unapproved drugs for life-threatening illnesses could negatively impact our business in the future.

A possible consequence of both activism and legislation in this area is the need for us to initiate an unanticipated expanded access program or to make our product candidates more widely available sooner than anticipated. We have limited resources and unanticipated trials or access programs could result in diversion of resources from our primary goals.

In addition, patients who receive access to unapproved drugs through compassionate use or expanded access programs have life-threatening illnesses and have exhausted all other available therapies. The risk for SAEs in this patient population is high, which could have a negative impact on the safety profile of our product candidates. This could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

We may be unable to effectively manage our programs.

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

We face potential product liability.

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

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

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

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

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

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

Despite our security measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to, among other things, damage from computer viruses, unauthorized access, ransomware, natural disasters, terrorism, war and telecommunication and electrical failures. Furthermore, the ongoing COVID-19 pandemic and the related disruptions to our business and our collaborators', contractors' and consultants' businesses may increase the risk of security incidents. If any cyberattack or data breach were to occur in the future and cause interruptions in our or our collaborators', contractors' or consultants' operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or the inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team and key employees, including our Chief Executive Officer and our President & Chief Operating Officer, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We do not maintain "key person" insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. Competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in pre-clinical or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or the loss of the services of any key employee or advisor could harm our business.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners, CROs and CDMOs. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Misconduct by these parties could include intentional failures to (i) comply with the regulations of the FDA, EMA or of other foreign regulatory authorities, (ii) provide accurate information to the FDA, EMA and other foreign regulatory authorities, (iii) comply with healthcare fraud and abuse laws and regulations in the United States and abroad, (iv) report financial information or data accurately or (v) disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a

failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions such as criminal and administrative penalties, damages, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of noncompliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

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

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

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

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

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

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

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

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

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

United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

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

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

- The federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties.

- The federal civil and criminal false claims laws and civil monetary penalty laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistle blower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistle blower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery.

- The anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program.

- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of,

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

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

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

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

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

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

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge and may not comply under one or more of such laws, regulations or guidance. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive share options as compensation for services provided, are found to be in violation of any of such laws or any

other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

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

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

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

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

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

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

- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, mis-classification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, fires and public health epidemics and pandemics, including the current COVID-19 global pandemic.

Risks related to our intellectual property

We may become subject to claims that we are infringing certain third-party patents, for example, patents relating to lentiviral vectors, or other third-party intellectual property rights, any of which may prevent or delay our development and commercialization efforts and have a material adverse effect on our business.

Our commercial success depends in part on avoiding infringing, misappropriating and otherwise violating the patents and other intellectual property and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, and administrative proceedings such as interferences, *inter partes* review and post grant review proceedings before the U.S. Patent and Trademark Office, or USPTO, and opposition proceedings before foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned or controlled by third parties, including our competitors, exist in the fields in which we are pursuing products and product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our products and product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we or our licensors are employing their proprietary technology without authorization. There may be third party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment relating to our products and product candidates and, because patent applications can take many years to issue, there may be currently pending third party patent applications which may later result in issued patents, in each case that our products and product candidates, their manufacture or use may infringe or be alleged to infringe.

Parties making patent infringement claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our products or product candidates. Defense of these claims, including demonstrating non-infringement, invalidity or unenforceability of the respective patent rights in question, regardless of their merit, is time-consuming, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. For example, in order to successfully challenge the validity of any U.S. patent in federal court, we would need to overcome a presumption of validity. This is a high burden requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, and we can provide no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. We may not have sufficient resources to bring these actions to a successful conclusion. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments.

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

commercially reasonable terms with respect to these patents, it could harm our business, financial condition, results of operations and prospects.

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

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

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

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

We are highly dependent on the intellectual property and data licensed to us by third parties, including technology related to the manufacture and use of our products and product candidates. We have in-licensed certain know-how and data from GSK and Telethon-OSR relating to Libmeldy, certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-IH, and certain other intellectual property for our clinical and pre-clinical programs. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

Our in-licensed intellectual property is often limited to particular fields and is often subject to certain retained rights. We may not have rights to use in-licensed intellectual property, data or know-how from one program in another program. As a result, we may not be free to commercialize certain of our products or product candidates in fields or territories of interest to us. Furthermore, if the licenses are not exclusive in territories of interest to us, we may be unable to prevent competitors from developing and commercializing competitive products in territories included in our licenses. Licenses (including sublicenses) to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business.

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

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the particular licensor may have the right to terminate such agreements. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse

effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected products and product candidates. Termination of our license agreements or reduction or elimination of our rights under them may result in our having to negotiate a new or reinstated agreement, which may not be available to us on equally favorable terms, or at all, which may mean we are unable to develop or commercialize the affected product or product candidate or cause us to lose our rights under the agreement. Any of the foregoing could have a material adverse effect on our business.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Even if we establish infringement, misappropriation or another violation of our intellectual property rights, a court may decide not to grant an injunction against the offender and instead award only monetary damages, which may not be an

adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our ADSs. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Any of the foregoing may have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

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

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

Changes in either the patent laws or the interpretation of the patent laws in the United States or other jurisdictions could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents.

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

is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible. Thereafter, the USPTO issued a guidance memorandum instructing USPTO examiners on the ramifications of the *Prometheus* and *Myriad* rulings and apply the *Myriad* ruling to natural products and principles including all naturally occurring nucleic acids. Certain claims of our in-licensed patent applications contain, and any future patents we may obtain may contain, claims that relate to specific recombinant DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties.

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

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

Risks related to ownership of our securities

The market price of our ADSs may be highly volatile and may fluctuate due to factors beyond our control.

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

- adverse results or delays in pre-clinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by our current or future collaborators to successfully develop and commercialize product candidates for which we are eligible to receive milestone and royalty payments;
- failure by us to adequately scale our manufacturing capabilities and commercial and sales organization to succeed in our commercialization efforts of Libmeldy;
- failure by us to succeed in our ongoing commercialization of Strimvelis;
- failure by us to gain broad insurance coverage and reimbursement for our product candidates, if approved;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial or other projections we may provide to the public;
- failure by us to meet or exceed the financial or other projections of the investment community;

- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- general economic, geopolitical and market conditions, including the significant disruptions to the U.S. and global economies and the related significant volatility and negative pressure in financial markets caused by the COVID-19 global pandemic, supply chain issues, inflationary pressures and the ongoing conflict in the Ukraine;
- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

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

If securities or industry analysts do not continue to publish research about our business or publish inaccurate or unfavorable research, our ADS price and trading volume could decline.

The trading market for our ADSs depends in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. In the event one or more analysts downgrade our ADSs or change their opinion of our ADSs, our ADS price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our ADS price or trading volume to decline.

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

Based upon our ordinary shares outstanding as of March 3, 2023, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 47.6% of our ordinary shares and ADSs. In computing the number of ordinary shares beneficially owned by a person, ordinary shares subject to options, or other rights held by such person that are currently exercisable or will become exercisable within 60 days of March 3, 2023, are considered outstanding. These ordinary shares, however, are not included in the number of shares outstanding as of March 3, 2023. (In other words, in calculating the beneficial ownership percentage, there are ordinary shares in the numerator that are not reflected in the denominator.) Depending on the level of attendance at our meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, and the approval of certain significant corporate transactions. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that our shareholders may believe are in their best interest as shareholders. Some of these persons or entities may have interests that are different than those of our other shareholders. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs were sold in our initial public offering and have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

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

Additional sales of our ADSs, or the perception that these sales could occur, could cause the market price of our ADSs to decline. If any of our large shareholders or members of our management team sell substantial amounts of ADSs in the public

market, or the market perceives that such sales may occur, the market price of our ADSs and our ability to raise capital through an issue of equity securities in the future could be adversely affected. Additionally, we filed a registration statement with the SEC and may issue securities in one or more underwritten transactions, in "at-the-market" offerings or in other transactions from time to time. If we were to issue such securities in the public market, the trading price of our ADSs could decline.

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

Holders of our publicly traded securities are holders of ADSs with underlying ordinary shares in a company incorporated under English law. Holders of ADSs are not treated as holders of our ordinary shares, unless they withdraw the ordinary shares underlying their ADSs in accordance with the deposit agreement and applicable laws and regulations. The depositary is the holder of the ordinary shares underlying the ADSs. Holders of ADSs therefore do not have any rights as holders of our ordinary shares, other than the rights that they have pursuant to the deposit agreement.

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

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

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

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

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

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

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York,

which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs.

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

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

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

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

Holders of our ADSs may not receive distributions on our ordinary shares represented by the ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

The depositary for the ADSs has agreed to pay to the holders of our ADSs the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses. Holders of our ADSs will receive these distributions in proportion to the number of our ordinary shares such holder's ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders of ADSs. We have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that holders of our ADSs may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available. These restrictions may have an adverse effect on the value of our ADSs.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be the sole source of gains to the holders of our ADSs and such holders may never receive a return on their investment.

Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be declared and paid. Therefore, we must have distributable profits before declaring and paying a dividend. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. As a result, capital appreciation, if any, on our ADSs will be the sole source of gains to the holders of our ADSs for the foreseeable future, and such holders may suffer a loss on their investment if they are unable to sell their ADSs at or above the price at which such holders purchased the ADSs.

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

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

We will continue to incur increased costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management is required to devote substantial time to new compliance initiatives.

As a public company listed on a U.S. Exchange, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel are required to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting and, once we are no longer a "smaller reporting company", we will be required to furnish an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In order to achieve and maintain compliance with Section 404, we have documented and evaluated our internal control over financial reporting, which is both costly and challenging. In this regard, we continue to dedicate internal resources, have engaged outside consultants and adopted a detailed work plan to continually assess and document the adequacy of internal control over financial reporting, taken steps to improve control processes as appropriate, validated through testing that controls are functioning as documented and have implemented a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk in any given year that we will not be able to conclude within the prescribed time frame that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. Moreover, if in the future we are required to obtain an opinion as to the effectiveness of our internal control over financial reporting and if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our ADSs could be negatively affected, and we could become subject to investigations by the SEC or other regulatory authorities or to shareholder litigation, which could have an adverse impact on the market price or our ADSs and cause us to incur additional expenses.

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

In February 2020, the UK Takeover Panel confirmed that we are not considered to be subject to The City Code on Takeovers and Mergers, or The Takeover Code, and, as a result, our shareholders are not entitled to the benefit of certain takeover offer protections provided under The Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted and which may operate to prohibit certain arrangements and courses of conduct considered customary in the United States. There are no provisions in our Articles of Association that replicate the provisions of The Takeover Code.

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

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

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

The principal differences include the following:

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

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ADSs.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, testing required to be conducted by us in connection with Section 404, and subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

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

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

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

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

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

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

Risks related to taxation

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

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

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

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

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

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

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

If we are a controlled foreign corporation, there could be adverse U.S. federal income tax consequences to certain U.S. holders.

Each “Ten Percent Shareholder” (as defined below) in a non-U.S. corporation that is classified as a “controlled foreign corporation,” or a CFC, for U.S. federal income tax purposes generally is required to include in income for U.S. federal tax purposes such Ten Percent Shareholder’s pro rata share of the CFC’s “Subpart F income” and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. Subpart F income generally includes dividends, interest, rents, royalties, global intangible low-taxed income, gains from the sale of securities and income from certain transactions with related parties. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in a CFC may be required to classify a portion of such gain as dividend income rather than capital gain. A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A “Ten Percent Shareholder” is a United States person (as defined by the Code) who owns or is considered to own 10% or more of the total combined voting power of all classes of stock entitled to vote of such corporation. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain.

We believe that we were not a CFC in the 2022 taxable year, but we may become a CFC in a subsequent taxable year. If we are classified as both a CFC and a passive foreign investment company, or PFIC (as discussed below), we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

If we are a PFIC there could be adverse U.S. federal income tax consequences to U.S. holders.

Under the Code, we will be a PFIC, for any taxable year in which (i) 75% or more of our gross income consists of passive income or (ii) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. holder holds our ordinary shares or ADSs, the U.S. holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

Based on the current and expected composition of our income and assets and the value of our assets, we believe that we were a PFIC for U.S. federal income tax purposes for our taxable year ended December 31, 2022. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future

and our corporate structure. The composition of our income and assets is also affected by the spending of the cash we raise in any offering.

In certain circumstances, a U.S. holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a "qualified electing fund," or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute "marketable" securities under the Code), which each require the inclusion of a pro rata share of our income on a current basis. Because it was possible we were a PFIC for the 2022 taxable year, we currently expect that we will provide the information necessary for U.S. holders to make a QEF Election. We may elect to provide such information on our website (www.ORTX.com). A U.S. holder would also be able to make a mark-to-market election with respect to our ordinary shares or ADSs as long as those shares or ADSs constitute marketable securities under the Code.

We may be unable to use UK net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable UK tax legislation.

As a UK incorporated and tax resident entity, we are subject to UK corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any UK corporation tax. As of December 31, 2022, we had cumulative carryforward tax losses of $633.4 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to UK profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus, broadly, an incremental 50% of UK taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a company that carries out extensive research and development activities, we seek to benefit from two UK research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are currently eligible for inclusion within these tax credit cash rebate claims.

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

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

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

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenue from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenue and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the UK research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

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

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

Risks related to our Domicile

Exchange rate fluctuations may materially affect our results of operations and financial condition.

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. Although we are headquartered in the United Kingdom, we also source research and development, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

Claims of U.S. civil liabilities may not be enforceable against us.

We are incorporated under English law. Certain members of our board of directors and senior management are non-residents of the United States, and a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether U.K. courts would entertain original actions brought in the United Kingdom against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of the United Kingdom as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that certain requirements are met. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement.

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain persons named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

General Risk Factors

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We could be subject to securities class action litigation.

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

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Facilities

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

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

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

Item 3. Legal Proceedings.

From time to time, we may be a party to litigation or subject to claims incident to the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, we currently believe that the final outcome of these ordinary course matters will not have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. As of December 31, 2022, we were not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information and Holders of Ordinary Shares and ADSs

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

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

Sales of Unregistered Securities

Not applicable.

Dividends

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

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

Information about Our Equity Compensation Plans

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

Item 6. Reserved.

Not applicable.

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

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

Business Overview

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

Since our inception in 2015, we have devoted substantially all of our resources to conducting research and development of our product candidates, in-licensing and acquiring rights to our product candidates, commercializing Libmeldy in Europe, business planning, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of equity securities, including American Depositary Shares ("ADSs") in our initial public offering ("IPO") and follow-on offering, ordinary shares in our private placement, and convertible preferred shares. We have also financed our operations through proceeds from our senior term facilities agreement (the "Amended Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), research grants from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., and proceeds associated two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program.

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

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

Our net losses were $150.7 million for the year ended December 31, 2022. As of December 31, 2022, we had an accumulated deficit of $900.9 million. As of December 31, 2022, we had cash, cash equivalents and marketable securities of $143.8 million. Our losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, government contracts or other strategic transactions. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all.

Recent Developments

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

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

Business update regarding COVID-19

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

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

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

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

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

Components of our results of operations

Product revenue

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

Collaboration revenue

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

Cost of product revenue

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

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

Operating expenses

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts and the development of our product candidates, and include:

- expenses incurred under agreements with third parties, including contract research organizations (CROs) that conduct research, pre-clinical activities and clinical trials on our behalf as well as contract manufacturing organizations that manufacture lentiviral vectors and cell-based drug products for use in our pre-clinical and clinical trials;
- expenses to acquire technologies to be used in research and development;
- salaries, benefits and other related costs, including share-based compensation expense, for personnel engaged in research and development functions;
- costs related to research and development performed associated with the Company's collaboration arrangement;
- costs of outside consultants, including their fees, share-based compensation and related travel expenses;
- the costs of laboratory supplies and acquiring, developing and manufacturing pre-clinical study and clinical trial materials;
- costs related to compliance with regulatory requirements;
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities, costs related to our collaboration agreements, and other operating costs;
- upfront, milestone and management fees for maintaining licenses under our third-party licensing agreements; and
- grant awards or other government incentives unrelated to income taxes that we earn that are recorded as an offset to the related research and development costs incurred.

We expense research and development costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid expenses or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. Amortization of the Strimvelis loss provision is also recorded as an offset to research and development expense.

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and contract manufacturing organizations in connection with our pre-clinical and clinical development activities. License fees and other costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. License fees and other costs incurred prior to designating a product candidate for development are included in unallocated costs. We do not allocate employee costs, costs associated with our early-stage discovery efforts, laboratory supplies, and facilities, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials or the manufacturing requirements to conduct those clinical trials. We expect that our research and development expenses will continue to decline due to the portfolio updates and workforce reduction we undertook in 2022 as well as the completion of certain activities to support an OTL-200 BLA submission.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, commercial, corporate and business development, and administrative

functions. Selling, general and administrative expenses also include professional fees for legal, patent, accounting, auditing, tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

Other income (expense), net

Interest income

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

Interest expense

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

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

Other income (expense)

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

Results of operations

Comparison of the years ended December 31, 2022 and 2021

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

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

Product revenue, net

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

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

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

Collaboration revenue

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

Cost of product revenue

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

Research and development expenses

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

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

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

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

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

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

Selling, general and administrative expenses

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

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

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

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

Other (expense) income, net

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

Liquidity and capital resources

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

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

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

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

Cash flows

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

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

Operating activities

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

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

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

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

Investing activities

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

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

Financing activities

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

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

Funding requirements

We expect our expenses and capital expenditures will remain consistent in the near term in connection with our ongoing activities as we advance the pre-clinical activities and clinical trials of our product candidates and as we:

- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of Libmeldy in Europe, and for any product candidates for which we may submit for and obtain marketing approval anywhere in the world;

- continue our development of our product candidates, including continuing our ongoing advanced registrational trials and supporting studies, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- perform research and development activities with respect to potential new product candidates;
- conduct investigational new drug application, or IND, and or clinical trial application, or CTA-enabling studies for our pre-clinical programs;
- initiate additional clinical trials and pre-clinical studies for our other product candidates;
- seek to identify and develop, acquire or in-license additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates, to support technology and process innovations and to support manufacturing of product to commercial scale;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even though we started generating Libmeldy product sales in 2022, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe our existing cash, cash equivalents, and marketable securities on hand, together with expected proceeds from sales of Libmeldy and the $34 million received in March 2023 from the 2023 private placement, will enable us to fund our operating expenses and capital expenditure requirements into 2025. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in greater detail in Note 2 to our consolidated financial statements in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

United Kingdom research and development tax credit

As a company that carries out research and development activities, we are able to submit tax credit claims from two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure Credit ("RDEC") program depending on eligibility. Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which we do not receive income.

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

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

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

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

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

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our prepaid and accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense.

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

Valuation of share-based compensation

We measure share-based awards granted to employees, non-employees and directors based on the fair value on the date of the grant and recognize compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. Forfeitures are accounted for as they occur. Generally, we issue share-based awards in the form of stock options with only service-based vesting conditions and record the expense for these awards using the straight-line method. We have also issued share-based awards with performance-based vesting conditions for which the expense is recognized when achievement of such performance conditions becomes probable.

The fair value of each share option is estimated on the date of grant using the Black-Scholes option pricing model. Until the completion of our initial public offering in November 2018, we had been a private company and lacked company-specific historical and implied volatility information for our shares. Therefore, we estimate our expected share price volatility based on the historical volatility of publicly traded peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded share price. The expected term of our share options has been determined utilizing the "simplified method" for awards that qualify as "plain-vanilla" options. Prior to the adoption of ASU 2018-07, the expected term of share options granted to non-employees was the contractual term. After adoption of ASU 2018-07, the expected term of share options granted to non-employees is determined in the same manner as share options granted to employees. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends on our ordinary shares and do not expect to pay any cash dividends in the foreseeable future.

Product revenue, net - Libmeldy

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

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

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

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

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

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

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

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

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

Off-balance sheet arrangements.

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

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

Interest rate sensitivity

As of December 31, 2022, we had cash, cash equivalents, marketable securities, and restricted cash of $148.0 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying UK and U.S. bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

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

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

Foreign currency exchange risk

The Company is exposed to foreign currency exchange risk because it currently operates in the United Kingdom and the United States. The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the ultimate parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises finance and expends cash in U.S. dollars and expects to continue to do so in the future. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency of the relevant entity at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net income (loss) for the respective periods. We recorded realized and unrealized foreign currency losses of $24.3 million and $1.2 million for the years ended December

31, 2022 and 2021. These foreign currency transaction gains and losses are included in other (expense) income in our consolidated statements of operations and comprehensive loss.

Assets and liabilities have been translated at the exchange rates at the balance sheet dates, while revenue and expenses are translated at the average exchange rates over the reporting period and shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net loss but are included in our foreign currency translation adjustment to other comprehensive loss, a component of shareholders' equity.

We do not currently engage in currency hedging activities in order to reduce our currency exposure, but we may begin to do so in the future. Instruments that may be used to hedge future risks include foreign currency forward and swap contracts. These instruments may be used to selectively manage risks, but there can be no assurance that we will be fully protected against material foreign currency fluctuations.

Item 8. Financial Statements and Supplementary Data.

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

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

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

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

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

Management's Annual Report on Internal Control Over Financial Reporting

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

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

Changes in Internal Control Over Financial Reporting

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

Item 9B. Other Information.

The following summary contains a description of material U.S. federal income tax and UK tax consequences of the acquisition, ownership and disposition of our ordinary shares or ADSs. This summary should not be considered a comprehensive description of all the tax considerations that may be relevant to beneficial owners of ADSs.

Material U.S. federal income tax considerations for U.S. holders

The following is a description of the material U.S. federal income tax consequences to the U.S. Holders described below of owning and disposing of our ordinary shares or ADSs. It is not a comprehensive description of all tax considerations that may be relevant to a particular person's decision to acquire securities. This discussion applies only to a U.S. Holder that holds our ordinary shares or ADSs as a capital asset for tax purposes (generally, property held for investment). In addition, it does not describe all of the tax consequences that may be relevant in light of a U.S. Holder's particular circumstances, including state and local tax consequences, estate tax consequences, alternative minimum tax consequences, the potential application of the Medicare contribution tax, and tax consequences applicable to U.S. Holders subject to special rules, such as:

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

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

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

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

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

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

iii. an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

iv. a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly, the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

PFIC Rules

If we are classified as a PFIC in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or
- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

Based on the current and expected composition of our income and assets and the value of our assets, we believe that we were a PFIC for U.S. federal income tax purposes for our taxable year ended December 31, 2022. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a "controlled foreign corporation" for any taxable year (see discussion below in "Controlled foreign corporation considerations"), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC or may be treated as a PFIC in the future.

If we are classified as a PFIC in any year with respect to which a U.S. Holder owns the ordinary shares or ADSs, we will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding years during which the U.S. Holder owns the ordinary shares or ADSs, regardless of whether we continue to meet the tests described above unless (i) we cease to be a PFIC and the U.S. Holder has made a "deemed sale" election under the PFIC rules, or (ii) the U.S. Holder makes a Qualified Electing Fund Election, or QEF Election, with respect to all taxable years during such U.S. Holders holding period in which we are a PFIC. If the "deemed sale" election is made, a U.S. Holder will be deemed to have sold the ordinary shares or ADSs the U.S. Holder holds at their fair market value and any gain from such deemed sale would be subject to the rules described below. After the deemed sale election, so long as we do not become a PFIC in a subsequent taxable year, the U.S. Holder's ordinary shares or ADSs with respect to which such election was made will not be treated as shares in a PFIC and the U.S. Holder will not be subject to the rules described below with respect to any "excess distribution" the U.S. Holder receives from us or any gain from an actual sale or other disposition of the ordinary shares or ADSs. U.S. Holders should consult their tax advisors as to the possibility and consequences of making a deemed sale election if we cease to be a PFIC and such election becomes available.

For each taxable year we are treated as a PFIC with respect to U.S. Holders, U.S. Holders will be subject to special tax rules with respect to any "excess distribution" such U.S. Holder receives and any gain such U.S. Holder recognizes from a sale or other disposition (including, under certain circumstances, a pledge) of ordinary shares or ADSs, unless (i) such U.S. Holder makes a QEF Election or (ii) our ordinary shares or ADSs constitute "marketable" securities, and such U.S. Holder makes a mark-to-market election as discussed below. Distributions a U.S. Holder receives in a taxable year that are greater than 125% of the average annual distributions a U.S. Holder received during the shorter of the three preceding taxable years or the U.S. Holder's holding period for the ordinary shares or ADSs will be treated as an excess distribution. Under these special tax rules:

- the excess distribution or gain will be allocated ratably over a U.S. Holder's holding period for the ordinary shares or ADSs;
- the amount allocated to the current taxable year, and any taxable year prior to the first taxable year in which we became a PFIC, will be treated as ordinary income; and
- the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years prior to the year of disposition or "excess distribution" cannot be offset by any net operating losses for such years, and gains (but not losses) realized on the sale of the ordinary shares or ADSs cannot be treated as capital, even if a U.S. Holder holds the ordinary shares or ADSs as capital assets.

Because it was possible that we were a PFIC for the 2022 taxable year, we currently expect that we will provide the information necessary for U.S. holders to make a QEF Election. We may elect to provide such information on our website (www.ORTX.com). In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are "marketable." Ordinary shares or ADSs will be marketable if they are "regularly traded" on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, we expect the mark-to-market election would be available to U.S. Holders if we are a PFIC. Each U.S. Holder should consult its tax advisor as to the whether a mark-to-market election is available or advisable with respect to the ordinary shares or ADSs.

A U.S. Holder that makes a mark-to-market election must include in ordinary income for each year an amount equal to the excess, if any, of the fair market value of the ordinary shares or ADSs at the close of the taxable year over the U.S. Holder's adjusted tax basis in the ordinary shares or ADSs. An electing holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder's adjusted basis in the ordinary shares or ADSs over the fair market value of the ordinary shares or ADSs at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains for prior years. Gains from an actual sale or other disposition of the ordinary shares or ADSs will be treated as ordinary income, and any losses incurred on a sale or other disposition of the shares will be treated as an ordinary loss to the extent of any net mark-to-market gains for prior years. Once made, the election cannot be revoked without the consent of the Internal Revenue Service, or the IRS, unless the ordinary shares or ADSs cease to be marketable.

However, a mark-to-market election generally cannot be made for equity interests in any lower-tier PFICs that we own, unless shares of such lower-tier PFIC are themselves "marketable." As a result, even if a U.S. Holder validly makes a mark-to-market election with respect to our ordinary shares or ADSs, the U.S. Holder may continue to be subject to the PFIC rules (described above) with respect to its indirect interest in any of our investments that are treated as an equity interest in a PFIC for U.S. federal income tax purposes. U.S. Holders should consult their tax advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an Annual Report containing such information as the U.S. Treasury may require. A U.S. Holder's failure to file the Annual Report will cause the statute of limitations for such U.S. Holder's U.S. federal income tax return to remain open with regard to the items required to be included in such report until three years after the U.S. Holder files the Annual Report, and, unless such failure

is due to reasonable cause and not willful neglect, the statute of limitations for the U.S. Holder's entire U.S. federal income tax return will remain open during such period. U.S. Holders should consult their tax advisors regarding the requirements of filing such information returns under these rules.

WE STRONGLY URGE OUR INVESTORS TO CONSULT THEIR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON THEIR INVESTMENTS IN OUR ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO THEIR INVESTMENT IN OUR ORDINARY SHARES OR ADSs.

Controlled foreign corporation considerations

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to include in income each year for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of certain types of income earned by the CFC, including "Subpart F income," "global intangible low-taxed income" and certain other income generated by the CFC, even if the CFC has made no distributions to its shareholders. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in the CFC may be required to classify a portion of such gain as dividend income rather than capital gain (see discussion below in "Taxation of distributions" regarding the tax treatment of dividend income). A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the Code) who owns or is considered to own 10% or more of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation.

We believe that we were not a CFC in the 2021 taxable year, though we have not made a determination regarding our CFC status in the current taxable year, and we may become a CFC in a subsequent taxable year. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. In addition, recent changes to the attribution rules relating to the determination of CFC status may make it difficult to determine our CFC status for any taxable year. It is possible that a shareholder treated as a U.S. person for U.S. federal income tax purposes will acquire, directly or indirectly, enough shares to be treated as a Ten Percent Shareholder. U.S. Holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a PFIC, we generally will not be treated as a PFIC with respect to those U.S. Holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Taxation of distributions

Subject to the discussion above under "PFIC rules," distributions paid on ordinary shares or ADSs, other than certain pro rata distributions of ordinary shares or ADSs, will generally be treated as dividends to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Because we may not calculate our earnings and profits under U.S. federal income tax principles, we expect that distributions generally will be reported to U.S. Holders as dividends. Subject to applicable limitations and the discussions above regarding concerns expressed by the U.S. Treasury, dividends paid to certain non-corporate U.S. Holders may be taxable at preferential rates applicable to "qualified dividend income" if we are a "qualified foreign corporation" and certain other requirements are met. However, the qualified dividend income treatment may not apply if we are treated as a PFIC with respect to the U.S. Holder. The amount of the dividend will be treated as foreign-source dividend income to U.S. Holders and will not be eligible for the dividends-received deduction generally available to U.S. corporations under the Code. Dividends will generally be included in a U.S. Holder's income on the date of the U.S. Holder's receipt of the dividend. The amount of any dividend income paid in foreign currency will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of actual *or constructive* receipt, regardless of whether the payment is in fact converted into U.S. dollars. If the dividend is converted into U.S. dollars on the date of receipt, a U.S. Holder should not be required to recognize foreign currency gain or loss in respect of the dividend income. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt. Such gain or loss would generally be treated as U.S.-source ordinary income or loss. The amount of any distribution of property other than cash (and other than certain pro rata distributions of ordinary shares or ADSs or rights to acquire ordinary shares or ADSs) will be the fair market value of such property on the date of distribution.

For foreign tax credit limitation purposes, our dividends will generally be treated as passive category income. Because no UK income taxes will be withheld from dividends on ordinary shares or ADSs, there will be no creditable foreign taxes associated with any dividends that a U.S. Holder will receive. The rules governing foreign tax credits are complex and U.S. Holders should therefore consult their tax advisers regarding the effect of the receipt of dividends for foreign tax credit limitation purposes.

Sale or other taxable disposition of ordinary shares and ADSs

Subject to the discussion above under "PFIC rules," gain or loss realized on the sale or other taxable disposition of ordinary shares or ADSs will be capital gain or loss and will be long-term capital gain or loss if the U.S. Holder held the ordinary shares or ADSs for more than one year. The amount of the gain or loss will equal the difference between the U.S. Holder's tax basis in the ordinary shares or ADSs disposed of and the amount realized on the disposition, in each case as determined in U.S. dollars. This gain or loss will generally be U.S.-source gain or loss for foreign tax credit purposes. The deductibility of capital losses is subject to limitations.

If the consideration received by a U.S. Holder is not paid in U.S. dollars, the amount realized will be the U.S. dollar value of the payment received determined by reference to the spot rate of exchange on the date of the sale or other disposition. However, if the ordinary shares or ADSs are treated as traded on an "established securities market" and you are either a cash basis taxpayer or an accrual basis taxpayer that has made a special election (which must be applied consistently from year to year and cannot be changed without the consent of the IRS), you will determine the U.S. dollar value of the amount realized in a non-U.S. dollar currency by translating the amount received at the spot rate of exchange on the settlement date of the sale. If you are an accrual basis taxpayer that is not eligible to or does not elect to determine the amount realized using the spot rate on the settlement date, you will recognize foreign currency gain or loss to the extent of any difference between the U.S. dollar amount realized on the date of sale or disposition and the U.S. dollar value of the currency received at the spot rate on the settlement date.

Information reporting and backup withholding

Payments of dividends and sales proceeds that are made within the United States or through certain U.S.-related financial intermediaries generally are subject to information reporting, and may be subject to backup withholding, unless (i) the U.S. Holder is a corporation or other exempt recipient or (ii) in the case of backup withholding, the U.S. Holder provides a correct taxpayer identification number and certifies that it is not subject to backup withholding on a duly executed Form W-9 or otherwise establishes an exemption.

Backup withholding is not an additional tax. The amount of any backup withholding from a payment to a U.S. Holder will be allowed as a credit against the U.S. Holder's U.S. federal income tax liability and may entitle the U.S. Holder to a refund, provided that the required information is timely furnished to the IRS.

Information with respect to foreign financial assets

Certain U.S. Holders who are individuals (and, under regulations, certain entities) may be required to report information relating to the ordinary shares or ADSs, subject to certain exceptions (including an exception for ordinary shares or ADSs held in accounts maintained by certain U.S. financial institutions), by filing IRS Form 8938 (Statement of Specified Foreign Financial Assets) with their federal income tax return. Such U.S. Holders who fail to timely furnish the required information may be subject to a penalty. Additionally, if a U.S. Holder does not file the required information, the statute of limitations with respect to tax returns of the U.S. Holder to which the information relates may not close until three years after such information is filed. U.S. Holders should consult their tax advisers regarding their reporting obligations with respect to their ownership and disposition of the ordinary shares or ADSs.

UK Taxation

The following is intended as a general guide to current UK tax law and HMRC published practice (which is not binding) applying as at the date of this Annual Report on Form 10-K (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs. It does not constitute legal or tax advice and does not purport to be a complete analysis of all UK tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief from UK taxation. It is written on the basis that the company is not (and will not) directly or indirectly at any time derive 75% or more of our qualifying asset value from UK land, and that it is and remains solely resident in the UK for tax purposes and will therefore be subject to the UK tax regime and not the U.S. tax regime save as set out above under "Material U.S. federal income tax considerations for U.S. Holders."

Except to the extent that the position of non-UK resident persons is expressly referred to, this guide relates only to persons who are resident (and in the case of individuals, domiciled or deemed domiciled) for tax purposes solely in the UK and do not have a permanent establishment, branch or agency (or equivalent) in any other jurisdiction with which the holding of the ADSs is connected, or UK Holders, who are absolute beneficial owners of the ADSs (and do not hold the ADSs through an Individual Savings Account or a Self-Invested Personal Pension) and any dividends paid in respect of the ADSs or underlying ordinary shares (where the dividends are regarded for UK tax purposes as that person's own income). It is assumed that for the purposes of this guide that a holder of an ADS is the beneficial owner of the underlying ordinary share and any dividend income for UK direct tax purposes.

This guide may not relate to certain classes of UK Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- brokers or dealers in securities or persons who hold ADSs otherwise than as an investment;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to UK taxation on a remittance basis or to whom split year treatment applies.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN UK TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN PARTICULAR CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-UK RESIDENT OR DOMICILED PERSONS OR PERSONS SUBJECT TO TAXATION IN ANY JURISDICTION OTHER THAN THE UK ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of UK tax.

Income Tax

An individual UK Holder may, depending on his or her particular circumstances, be subject to UK tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to UK income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade, profession or vocation in the UK through a permanent establishment, branch or agency to which the ADSs are attributable. There are certain exceptions for trading in the UK through independent agent, such as some brokers and investment managers.

Dividend income is treated as the top slice of the total income chargeable to UK income tax for an individual UK Holder. An individual UK Holder who receives a dividend in the 2022/2023 tax year will be entitled to a tax-free allowance of £2,000. Income within the dividend allowance counts towards an individual's basic or higher rate limits and may, therefore, affect the level of personal allowance to which they are entitled. Dividend income in excess of this tax-free allowance will (subject to the availability of any income tax personal allowance) be charged at 8.75% to the extent the excess amount falls within the basic rate band, 33.75% to the extent the excess amount falls within the higher rate band, and 39.35% to the extent the excess amount falls within the additional rate band. The UK government has announced that the dividend tax-free allowance of £2,000 will be reduced to £1,000 with effect from April 2023 for the tax year 2023/2024 and to £500 with effect from April 2024 for the tax year 2024/2025 and thereafter.

Corporation tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to UK corporation tax on dividends received from the company unless it carries on (whether solely or in partnership) a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable.

Corporate UK Holders should not be subject to UK corporation tax on any dividend received from the company so long as the dividends qualify for exemption, which should be the case, although certain conditions must be met. It should be noted that the exemptions, whilst of wide application, are not comprehensive and are subject to anti-avoidance rules in relation to a dividend. If the conditions for the exemption are not satisfied, or such anti-avoidance provisions apply, or such UK Holder elects for an otherwise exempt dividend to be taxable, UK corporation tax will be chargeable on the amount of any dividends

(at the current rate of 19% for the tax year 2022/2023, rising to 25% in the tax year 2023/2024 for companies with profits of more than £250,000, whilst the rate of 19% will apply to companies with profits not exceeding £50,000 with a tapered rate applying to profits between £50,000 and £250,000).

Chargeable gains

A disposal or deemed disposal of ADSs by a UK Holder may, depending on the UK Holder's circumstances and subject to any available exemptions or reliefs (such as the annual exemption), give rise to a chargeable gain or an allowable loss for the purposes of UK capital gains tax and corporation tax on chargeable gains.

If an individual UK Holder who is subject to UK income tax at either the higher or the additional rate is liable to UK capital gains tax on the disposal of ADSs, the applicable rate will be 20% (for the tax year 2022/2023). For an individual UK Holder who is subject to UK income tax at the basic rate and liable to UK capital gains tax on such disposal, the applicable rate would be 10% (for the tax year 2022/2023), save to the extent that any capital gains when aggregated with the UK Holder's other taxable income and gains in the relevant tax year exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (for the tax year 2022/2023).

If a corporate UK Holder becomes liable to UK corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of UK corporation tax would apply (currently at 19% for the tax year 2022/2023, rising to 25% in the tax year 2023/2024 for companies with profits of more than £50,000, whilst the rate of 19% will apply to companies with profits not exceeding £250,000 with a tapered rate applying to profits between £50,000 and £250,000).

A holder of ADSs which is not resident for tax purposes in the UK should not normally be liable to UK capital gains tax or corporation tax on chargeable gains on a disposal (or deemed disposal) of ADSs, unless the person is carrying on (whether solely or in partnership) a trade, profession or vocation UK through a branch or agency (or, in the case of a corporate holder of ADSs, through a permanent establishment) to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the UK for a period of less than five years and who disposes of ADSs during that period of temporary non-residence may be liable on his or her return to the UK (or upon ceasing to be regarded as resident outside the UK for the purposes of double taxation treaty) to UK tax on any capital gain realized (subject to any available exemption or relief).

Stamp duty and stamp duty reserve tax

The discussion below relates to the holders of our ordinary shares or ADSs wherever resident, however it should be noted that special rules may apply to certain persons such as market makers, brokers, dealers or intermediaries.

Issue of Ordinary Shares

As a general rule, no UK stamp duty or stamp duty reserve tax (or SDRT) is payable on the issue of underlying ordinary shares in the company.

Transfers of Ordinary Shares

An unconditional agreement to transfer ordinary shares will normally give rise to a charge to SDRT at the rate of 0.5% of the amount or value of the consideration payable for the transfer. The purchaser of the shares is liable for the SDRT. Transfers of ordinary shares in certificated form are generally also subject to stamp duty at the rate of 0.5% of the amount or value of the consideration given for the transfer (rounded up to the next £5.00). Stamp duty is normally paid by the purchaser. The charge to SDRT will be canceled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

Clearance Services and Depositary Receipts

Under current UK legislation, an issue or transfer of ordinary shares or an unconditional agreement to transfer ordinary shares to a clearance service or a depositary receipt system (including, to a nominee or agent for, a person whose business is or includes the issue of depositary receipts or the provision of clearance services) will generally be subject to SDRT (and, in the case of transfers, where the transfer is effected by a written instrument, stamp duty) at a higher rate of 1.5% of the amount or value of the consideration given for the transfer unless the clearance service has made and maintained an election under section 97A of the UK Finance Act 1986, or a section 97A election. It is understood that HMRC regards the facilities of DTC as a clearance service for these purposes and we are not aware of any section 97A election having been made by the DTC.

However, based on current published HMRC practice following European Union case law in respect of the European Council Directives 69/335/EEC and 2009/7/EC, or the Capital Duties Directives, no SDRT is generally payable in respect of such an issue of ordinary shares and no SDRT or stamp duty is generally payable in respect of such a transfer of ordinary shares where such transfer is an integral part of an issue of share capital. This position was reaffirmed by HMRC in their January 2021 Newsletter where they confirmed that the SDRT 1.5% charge on issues (or transfers integral to capital raising) remained disapplied under the terms of the European Union (Withdrawal) Act 2018 following the end of the transition period and that this would remain the position unless stamp taxes on shares legislation was amended.

Any stamp duty or SDRT payable on a transfer of ordinary shares to a depositary receipt system or clearance service will in practice generally be paid by the transferors or participants in the clearance service or depositary receipt system. Specific professional advice should be sought before incurring or reimbursing the costs of a 1.5% charge.

Transfers of ADSs

No UK SDRT or stamp duty is required to be paid in respect of the issue of or an agreement to transfer ADS (including by way of a paperless transfer of ADSs through the facilities of DTC).

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 11. Executive Compensation.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 14. Principal Accounting Fees and Services.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

The following documents are filed as part of this Annual Report on Form 10-K:

(a) (1) *Financial Statements*:

The financial statements required by this item are submitted in a separate section beginning on page F-1 of this Report, as follows:

(a) (2) *Financial Statement Schedules*:

Not applicable.

(a) (3) *Exhibits*:

The Exhibits which are filed as part of this Annual Report or which are incorporated by reference are set forth in the Exhibit Index hereto.

EXHIBIT INDEX

Exhibit Number	Description	Incorporated by Reference herein from Form or Schedule	Exhibit	File Date	File Number
2.1†	Asset Purchase and License Agreement, among the registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Ltd., dated April 11, 2018 (Schedules, exhibits, and similar supporting attachments are omitted pursuant to Item 601(b)(2) of Regulation S-K. The registrant agrees to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request).	Form F-1	2.1	Oct. 4, 2018	333-227698
3.1	Articles of Association of Orchard Therapeutics plc	Form 8-K	3.1	Jun. 19, 2020	001-38722
4.1	Deposit Agreement	Form 20-F	2.1	Mar. 22, 2019	001-38722
4.2*	Amendment No. 1 to Deposit Agreement				001-38722
4.3	Form of American Depositary Receipt (included in Exhibit 4.1)	Form 20-F	2.2	Mar. 22, 2019	001-38722
4.4	Investment and shareholders' agreement between the registrant and the shareholders named therein, dated August 2, 2018, as amended.	Form F-1	10.1	Jun. 3, 2019	333-231916

4.5*	Description of the registrant's securities.				001-38722
4.6	At-the-Market Letter Agreement	Form F-6	(b)	Feb. 10, 2023	001-38722
4.7	Form of Warrant	Form 8-K	4.1	Mar. 6, 2023	001-38722
10.1#	2016 Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan, as amended.	Form F-1	10.2	Oct. 4, 2018	333-227698
10.2#	2018 Share Option and Incentive Plan.	Form 20-F	4.3	Mar. 22, 2019	001-38722
10.3#	2018 Employee Share Purchase Plan.	Form F-1/A	10.10	Oct. 23, 2018	333-227698
10.4#	Forms of award agreements under the 2018 Share Option and Incentive Plan.	Form 10-K	10.13	Feb. 27, 2020	001-38722
10.5#	2019 Short-Term Incentive Plan.	Form 10-Q	10.1	May 7, 2020	001-38722
10.6#	2020 Inducement Equity Plan and forms of award agreements thereunder.	Form S-8	99.2	Aug. 6 2020	333-241646
10.7#	Form of Deed of Indemnity between the registrant and each of its directors and executive officers.	Form F-1	10.6	Oct. 4, 2018	333-227698
10.8	Deed of Novation, among the registrant, Glaxo Group Limited, GlaxoSmithKline Intellectual Property Development Limited, GlaxoSmithKline S.p.A., Fondazione Telethon and Ospedale San Raffaele (in its own capacity and as successor in interest to Fondazione Centro San Raffaele Del Monte Tabor), dated April 5, 2018	Form F-1	10.4	Oct. 4, 2018	333-227698
10.9	Research and Development Collaboration and License Agreement, among Glaxo Group Limited, Fondazione Telethon and Fondazione Centro San Raffaele del Monte Tabor, dated October 15, 2010, as amended	Form F-1	10.5	Oct. 4, 2018	333-227698
10.10	Securities Purchase Agreement dated February 4, 2021, among Orchard Therapeutics plc and the Purchasers named therein	Form 10-Q	10.1	May 13, 2021	001-38722
10.11	Lease Agreement, dated April 5, 2022, among 245 Hammersmith Road Nominee Limited, 245 Hammersmith Road Nominee 2 Limited, 245 Hammersmith Road Partnership and Orchard Therapeutics (Europe) Limited	Form 10-Q	10.1	Aug. 4, 2022	001-38722
10.12†	License and Development Agreement, between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016, as amended.	Form F-1	10.8	Oct. 4, 2018	333-227698
10.13††	Amendment Nos. 5 and 6 to License and Development Agreement, between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016.	Form 10-Q	10.2	May 7, 2020	001-38722
10.14*	Senior Term Facilities Agreement, dated May 24, 2019, as amended and restated on January 30, 2023, among Orchard Therapeutics plc, the entities listed as original guarantors therein,				001-38722

	MidCap Financial (Ireland) Limited, and the additional lenders party thereto from time to time.				
10.15#	Amended and Restated Employment Agreement, dated October 4, 2022, among Orchard Therapeutics plc, Orchard Therapeutics North America and Frank Thomas	Form 8-K	10.1	Oct. 6, 2022	001-38722
10.16#	Contract of Employment between Orchard Therapeutics (Europe) Limited and Hubert Gaspar, dated January 8, 2018, as amended, effective May 24, 2019.	Form 10-K	10.16	Feb. 27, 2020	001-38722
10.17#	Variation to Contract of Employment, dated March 18, 2020, between Orchard Therapeutics (Europe) Limited and Hubert Gaspar, M.D., Ph.D.	Form 8-K	10.3	Mar. 20, 2020	001-38722
10.18††	Manufacturing and Technology Development Master Agreement, between Orchard Therapeutics (Europe) Limited and MolMed S.p.A., dated July 2, 2020.	Form 10-Q	10.1	Aug. 6, 2020	001-38722
10.19*	Amendment 1 to the Manufacturing and Technology Development Master Agreement, between Orchard Therapeutics (Europe) Limited and AGC Biologics S.p.A. (formerly MolMed S.p.A), dated December 7, 2022				001-38722
10.20	Securities Purchase Agreement dated March 6, 2023, by and among Orchard Therapeutics plc and the Purchasers named therein.	Form 8-K	10.1	Mar. 6, 2023	001-38722
21.1*	List of Subsidiaries.				
23.1*	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm				
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
101.INS*	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document)				

101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104*	Cover Page Interactive Data File (embedded within the Inline XBRL document).

* Filed herewith.

† Confidential treatment has been granted for portions of this exhibit. These portions have been omitted from the registration statement and filed separately with the United States Securities and Exchange Commission.

†† Portions of this exhibit (indicated by asterisks) were omitted in accordance with the rules of the Securities and Exchange Commission

# Indicates a management contract or any compensatory plan, contract or arrangement.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

ORCHARD THERAPEUTICS PLC

Date: March 14, 2023

By: /s/ Bobby Gaspar
Bobby Gaspar
Chief Executive Officer

POWER OF ATTORNEY

We, the undersigned officers and directors of Orchard Therapeutics plc, hereby severally constitute and appoint Bobby Gaspar and Frank E. Thomas, and each of them singly (with full power to each of them to act alone), our true and lawful attorneys-in-fact and agents, with full power of substitution and re-substitution in each of them for him and in his name, place and stead, and in any and all capacities, to sign for us and in our names in the capacities indicated below any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto and other documents in connection therewith, with the U.S. Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite or necessary to be done in and about the premises, as full to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents or any of them, or their or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Annual Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Bobby Gaspar Bobby Gaspar	Chief Executive Officer and Director (Principal Executive Officer)	March 14, 2023
/s/ Frank E. Thomas Frank E. Thomas	President and Chief Operating Officer (Principal Financial Officer and Principal Accounting Officer)	March 14, 2023
/s/ James A. Geraghty James A. Geraghty	Chairman of the Board of Directors	March 14, 2023
/s/ Steven M. Altschuler Steven M. Altschuler, M.D.	Director	March 14, 2023
/s/ Joanne T. Beck Joanne T. Beck, Ph.D.	Director	March 14, 2023
/s/ John Curnutte John Curnutte, M.D., Ph.D.	Director	March 14, 2023
/s/ Marc Dunoyer Marc Dunoyer	Director	March 14, 2023
/s/ Charles A. Rowland, Jr. Charles A. Rowland, Jr.	Director	March 14, 2023
/s/ Alicia Secor Alicia Secor	Director	March 14, 2023

INDEX TO THE FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Shareholders of Orchard Therapeutics plc

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Orchard Therapeutics plc and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations and comprehensive loss, of shareholders equity and of cash flows for the years then ended, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued External Research and Development Expenses

As described in Notes 2 and 8 to the consolidated financial statements, the Company has entered into various research and development contracts. When billing terms under these contracts do not coincide with the timing of when the work is performed, management is required to make estimates of outstanding obligations to those third parties. Within accrued expenses and other current liabilities, total accrued external research and development expenses amounted to $11.2 million as of December 31, 2022. Any accrual estimates are based on a number of factors, including management's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period.

The principal considerations for our determination that performing procedures relating to accrued external research and development expenses is a critical audit matter are (i) the significant judgment by management in developing the estimate and (ii) a high degree of auditor judgment, subjectivity, and effort in performing procedures and evaluating management's factors related to the progress towards completion of the research and development activities, the related invoicing to date under the contracts and communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included, among others, (i) testing management's process for developing the estimate of accrued external research and development expenses, and for a sample of contracts, (ii) evaluating the appropriateness of the methods used by management to develop the estimate; (iii) testing the completeness and accuracy of the underlying data used in the estimate; and (iv) evaluating the reasonableness of management's factors related to the progress towards completion of the research and development activities. Evaluating the reasonableness of management's factors related to the progress towards completion of the research and development activities involved testing, on a sample basis, invoicing to date under the contracts and communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced.

/s/PricewaterhouseCoopers LLP

Boston, Massachusetts
March 14, 2023

We have served as the Company's auditor since 2019.

Orchard Therapeutics plc
Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 68,424	$ 55,912
Marketable securities	75,326	164,195
Accounts receivable	8,467	1,480
Prepaid expenses and other current assets	9,986	23,011
Research and development tax credit receivable	5,942	30,723
Total current assets	168,145	275,321
Non-current assets:		
Operating lease right-of-use-assets	22,774	24,316
Property and equipment, net	8,138	4,767
Restricted cash	4,215	4,266
Intangible assets, net	3,560	4,149
Other assets	12,075	9,590
Total non-current assets	50,762	47,088
Total assets	$ 218,907	$ 322,409
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 9,318	$ 10,008
Accrued expenses and other current liabilities	34,437	24,318
Deferred revenue	959	346
Operating lease liabilities	6,424	7,335
Notes payable, current	9,429	786
Total current liabilities	60,567	42,793
Notes payable, long-term	22,991	32,086
Deferred revenue, net of current portion	10,315	12,519
Operating lease liabilities, net of current portion	19,246	19,278
Other long-term liabilities	7,524	5,783
Total liabilities	120,643	112,459
Commitments and contingencies (Note 17)		
Shareholders' equity:		
Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 of shares at December 31, 2022 and 2021, respectively; Issued and outstanding — 126,947,225 and 125,674,095 shares at December 31, 2022 and 2021, respectively.	16,419	16,253
Additional paid-in capital	956,711	940,675
Accumulated other comprehensive income	26,018	3,246
Accumulated deficit	(900,884)	(750,224)
Total shareholders' equity	98,264	209,950
Total liabilities and shareholders' equity	$ 218,907	$ 322,409

The accompanying notes are an integral part of these consolidated financial statements.

Orchard Therapeutics plc
Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share amounts)

	For the Year Ended December 31,	
	2022	2021
Product revenue, net	$ 20,610	$ 700
Collaboration revenue	2,045	975
Total revenues	22,655	1,675
Costs and operating expenses		
Cost of product revenue	6,771	226
Research and development	93,847	86,977
Selling, general and administrative	49,125	54,905
Total costs and operating expenses	149,743	142,108
Loss from operations	(127,088)	(140,433)
Other (expense) income:		
Interest income	1,543	412
Interest expense	(3,079)	(2,497)
Other (expense) income, net	(24,410)	(1,238)
Total other (expense) income, net	(25,946)	(3,323)
Net loss before income tax	(153,034)	(143,756)
Income tax (expense) benefit	2,374	(828)
Net loss attributable to ordinary shareholders	$ (150,660)	$ (144,584)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.18)	$ (1.17)
Weighted average number of ordinary shares outstanding—basic and diluted	127,975,062	123,963,762
Other comprehensive income (loss)		
Foreign currency translation adjustment	22,838	3,124
Unrealized loss on marketable debt securities	(66)	(251)
Total other comprehensive income (loss)	22,772	2,873
Total comprehensive loss	$ (127,888)	$ (141,711)

The accompanying notes are an integral part of these consolidated financial statements.

Orchard Therapeutics plc
Consolidated Statements of Shareholders' Equity
(In thousands, except share amounts)

	Ordinary shares					
	Shares	Amount	Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
Balance at December 31, 2020	**98,283,603**	**$ 12,507**	**$ 771,194**	**$ 373**	**$ (605,640)**	**$ 178,434**
Share-based compensation expense	—	—	22,536	—	—	22,536
Exercise of share options	1,727,254	224	2,515	—	—	2,739
Issuance of ESPP shares	232,340	30	534	—	—	564
Vesting of restricted share units, net of shares withheld for taxes	64,647	9	(401)	—	—	(392)
Sale of voting and non-voting ordinary shares, net of issuance costs of $6,355	24,115,755	3,310	140,335	—	—	143,645
Ordinary shares issued as part of consulting agreement	22,758	3	(3)	—	—	—
Ordinary shares issued as part of collaboration agreement	1,227,738	170	3,965	—	—	4,135
Foreign currency translation	—	—	—	3,124	—	3,124
Unrealized loss on marketable debt securities	—	—	—	(251)	—	(251)
Net loss	—	—	—	—	(144,584)	(144,584)
Balance at December 31, 2021	**125,674,095**	**$ 16,253**	**$ 940,675**	**$ 3,246**	**$ (750,224)**	**$ 209,950**
Share-based compensation expense	—	—	16,010	—	—	16,010
Exercise of share options	699,234	91	(90)	—	—	1
Issuance of ESPP shares	544,442	72	139	—	—	211
Vesting of restricted share units, net of shares withheld for taxes	24,202	3	(22)	—	—	(19)
Ordinary shares issued as part of consulting agreement	5,252	—	(1)	—	—	(1)
Foreign currency translation	—	—	—	22,838	—	22,838
Unrealized loss on marketable debt securities	—	—	—	(66)	—	(66)
Net loss	—	—	—	—	(150,660)	(150,660)
Balance at December 31, 2022	**126,947,225**	**$ 16,419**	**$ 956,711**	**$ 26,018**	**$ (900,884)**	**$ 98,264**

The accompanying notes are an integral part of these consolidated financial statements.

Orchard Therapeutics plc
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,	
	2022	2021
Cash flows from operating activities		
Net loss attributable to ordinary shareholders	$ (150,660)	$ (144,584)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	2,741	2,327
Share-based compensation	16,010	22,536
Non-cash interest expense	372	392
Amortization of provision on loss contract	(274)	(1,037)
Deferred income taxes	(3,283)	1,131
Amortization of premium (discount) on marketable securities	(305)	1,514
Unrealized foreign currency and other non-cash adjustments	23,208	9,687
Changes in operating assets and liabilities:		
Accounts receivable	(7,420)	(624)
Research and development tax credit receivable	22,568	(13,920)
Prepaid expenses, other current assets, and other assets	5,053	(5,209)
Operating leases, right-of-use-assets	5,431	5,938
Accounts payable, accrued expenses, and other current liabilities	13,642	(9,452)
Deferred revenue	(272)	13,122
Other long-term liabilities	2,154	34
Operating lease liabilities	(4,952)	(6,952)
Net cash used in operating activities	$ (75,987)	$ (125,097)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	201,389	234,732
Purchases of marketable securities	(112,281)	(263,878)
Receipt of funds from construction deposit	7,966	216
Payments on intangible assets	—	(887)
Purchases of property and equipment	(6,514)	(2,348)
Net cash provided by (used in) investing activities	$ 90,560	$ (32,165)
Cash flows from financing activities		
Proceeds from modification of credit facility, net of debt issuance costs paid	—	7,375
Proceeds from employee equity plans	212	3,303
Payment of taxes on restricted stock vesting	(19)	(392)
Proceeds from issuance of shares as part of collaboration agreement	—	4,135
Proceeds from the issuance of ordinary shares in private placement	—	150,000
Payment of placement agent fees and offering costs	(100)	(6,355)
Repayment of notes payable	(786)	—
Net cash (used in) provided by financing activities	$ (693)	$ 158,066
Effect of exchange rate changes on cash	(1,419)	(27)
Net increase in cash, cash equivalents and restricted cash	$ 12,461	$ 777
Cash, cash equivalents, and restricted cash —beginning of year	60,178	59,401
Cash, cash equivalents, and restricted cash —end of year	$ 72,639	$ 60,178
Supplemental disclosure of non-cash activities		
Intangible assets and property and equipment in accounts payable and accrued expenses	60	2,589
Supplemental disclosure of cash flow information		
Lease assets obtained in exchange for new operating lease liabilities	4,912	552
Changes to operating lease right-of-use assets and liabilities from amendments	530	—
Cash paid for interest	2,648	2,103
Cash paid for taxes	157	1,651

The accompanying notes are an integral part of these consolidated financial statements.

1. Nature of the Business and Liquidity

Orchard Therapeutics plc (the "Company") is a global gene therapy company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. The Company's *ex vivo* autologous hematopoietic stem cell ("HSC") gene therapy approach utilizes genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Company has a portfolio that includes a commercial-stage product and research and development-stage product candidates.

The Company is a public limited company incorporated pursuant to the laws of England and Wales. The Company has American Depositary Shares ("ADSs") registered with the U.S. Securities and Exchange Commission (the "SEC"). The ADSs were listed on the Nasdaq Global Select Market on October 31, 2018 and were transferred to the Nasdaq Capital Market on September 13, 2022. As of December 31, 2022, each holder of ordinary shares and ADSs is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. The Company did not declared any dividends in 2022 or 2021.

Effective March 10, 2023, the Company enacted a ratio change wherein each ADS listed on the Nasdaq Capital Market is worth ten ordinary shares.

On February 9, 2021, the Company issued and sold (i) 20,900,321 ordinary shares, nominal value £0.10 per share, at a purchase price of $6.22 per share (the "Purchase Price"), which was the closing sale price of the Company's ADSs on the Nasdaq Global Select Market on February 4, 2021, and (ii) 3,215,434 non-voting ordinary shares, nominal value £0.10 per share, at the Purchase Price (together (i) and (ii) the "2021 Private Placement"). The 2021 Private Placement resulted in net proceeds to the Company of $143.6 million after deducting placement agent fees of $6.0 million and other issuance costs of $0.4 million. As of December 31, 2021, all outstanding non-voting shares have been converted to voting ordinary shares.

In January 2022, the Company began to generate revenue from product sales of Libmeldy™ in Europe following the approval of Libmeldy by the European Commission in December 2020 for the treatment of early onset metachromatic leukodystrophy ("MLD"), characterized by biallelic mutations in the arylsulfatase-A ("ARSA") gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

On March 6, 2023, the Company entered into a Securities Purchase Agreement pursuant to which the Company agreed to sell ordinary shares, non-voting ordinary shares, and warrants to purchase to purchase ordinary shares or non-voting ordinary shares in an unregisterd offering (the "2023 Private Placement"). The 2023 Private Placement consists of two closings. On March 10, 2023, the Company completed the initial closing and issued and sold (i) 56,666,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share and (ii) warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The initial closing of the 2023 Private Placement resulted in gross proceeds of approximately $34.0 million. Refer to Footnote 19 for further discussion around the 2023 Private Placement.

The Company's business is subject to risks and uncertainties common to development-stage companies in the biotechnology industry. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's technology will be obtained, that any products developed will obtain necessary government regulatory approval or that any products, if approved, will be commercially viable. The Company operates in an environment of rapid technological innovation and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and service providers. Even if the Company's product development efforts are successful in gaining regulatory approval, it is uncertain when, if ever, the Company will realize significant revenue from product sales. The future developments of the COVID-19 pandemic may also directly or indirectly impact the Company's business, including impacts due to travel restrictions, supply chain disruptions, business closures, and other measures.

Through December 31, 2022, the Company funded its operations with proceeds from the sale of equity securities, including ADSs in the Company's initial public offering ("IPO") and follow-on offering, ordinary shares in the private placement, and convertible preferred shares. The Company has also financed its operations through proceeds from the Company's senior term facilities agreement with MidCap Financial (Ireland) Limited, research grants from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from the Company's collaboration agreement and share purchase agreement with Pharming Group N.V., proceeds from the sales of the Company's Libmeldy product, and reimbursements associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and

development tax credit (“SME”) program and the Research and Development Expenditure (“RDEC”) program. The Company has incurred recurring losses since its inception and expects to continue to generate operating losses for the foreseeable future.

The Company expects that its cash, cash equivalents, and marketable securities on hand as of December 31, 2022, of $143.8 million, together with expected proceeds from sales of Libmeldy and the $34 million received in March 2023 from the 2023 Private Placement, will be sufficient to fund its operations and capital expenditure requirements for at least twelve months from the date of filing of this Annual Report on Form 10-K. The Company will seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances, and marketing, distribution or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and may not be able to enter into collaborations or other arrangements. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

2. Summary of Significant Accounting Policies

Basis of presentation

The accompanying consolidated financial statements have been prepared in conformity with U.S. generally accepted accounting principles ("GAAP") and include the accounts of the Company and its wholly owned subsidiaries, after elimination of all intercompany accounts and transactions. Any reference in these notes to applicable guidance is meant to refer to authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification (“ASC”) and as amended by Accounting Standards Updates (“ASU”) of the Financial Accounting Standards Board (“FASB”).

Amounts reported are based in thousands, except percentages, per share amounts or as otherwise noted. As a result, certain totals may not sum due to rounding.

Principles of consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Use of estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the research and development tax credit receivable, share-based compensation, collaboration agreement milestones, variable consideration in revenue recognition, operating lease assets and liabilities, and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company’s estimates.

Concentration of credit risk and of significant suppliers

The Company has no significant off-balance sheet risk, such as foreign currency contracts, options contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents, marketable securities, and receivables.

The Company invests its excess cash, in line with its investment policy, in money market funds and high credit quality debt instruments. The Company's cash is deposited in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships or entities for which it has a receivable.

The Company is dependent upon a third-party contract manufacturer to develop, manufacture, and supply certain raw materials and conduct manufacturing activities for certain research and development and commercial programs. The disruption of the supply of raw materials and manufacturing activities could adversely affect the Company's operations. The

Company believes that its relationship with this manufacturer is satisfactory and has contingency plans in place to mitigate any adverse effects around the loss of this contract manufacturer.

Foreign currency

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. Dollar are translated into U.S. Dollars using period-end exchange rates for assets and liabilities, historical exchange rates for shareholders' equity and weighted average exchange rates for operating results. Unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar, Pounds sterling, and Euro exchange rates. Translation gains and losses are included in accumulated other comprehensive income (loss) in shareholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations. The Company recorded realized and unrealized foreign currency transaction losses of $24.3 million and of $1.2 million for the years ended December 31, 2022 and 2021, respectively, which is included in other income (expense) in the statements of operations and comprehensive loss.

Segment information

The Company operates in a single segment focusing on researching, developing and commercializing potentially curative gene therapies. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, the results of the Company's operations are reported on a consolidated basis for the purposes of segment reporting.

All material long-lived assets of the Company reside in the United States or United Kingdom. The Company had property and equipment, net, of $7.5 million and $0.6 million located in the United Kingdom and United States, respectively, as of December 31, 2022. The Company had property and equipment, net, of $3.6 million and $1.2 million located in the United Kingdom and United States, respectively, as of December 31, 2021. The Company had right-of-use assets in the United States and United Kingdom of $11.2 million and $11.6 million, respectively, as of December 31, 2022. The Company had right-of-use assets in the United States and United Kingdom and European Union of $12.5 million and $11.8 million, respectively, as of December 31, 2021.

Cash equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at the date of acquisition to be cash equivalents.

Marketable securities

Marketable securities consist of investments with original maturities greater than ninety days from the date of acquisition. The Company has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio of investments as available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices or other observable inputs. Unrealized gains and losses are recorded as a component of other comprehensive income (loss). Realized gains and losses are determined on a specific identification basis and are included in other income (loss). Amortization and accretion of discounts and premiums is also recorded in other income (loss).

When the fair value is below the amortized cost of the asset an estimate of expected credit losses is made, the estimate is limited to the amount by which fair value is less than amortized cost. The credit-related impairment amount is recognized in the consolidated statements of operations and the remaining impairment amount and unrealized gains are reported as a component of accumulated other comprehensive income (loss) in shareholders' equity. Credit losses are recognized through the use of an allowance for credit losses account and subsequent improvements in expected credit losses are recognized as a reversal of the allowance account. If the Company has the intent to sell the security or it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis the allowance for credit loss is written off and the excess of the amortized cost basis of the asset over its fair value is recorded in the consolidated statements of operations.

Accounts receivable

Accounts receivable arise from product revenue and amounts due from the Company's collaboration partners and have payment terms that generally require payment within 30 to 90 days. For some Libmeldy customers, our payment terms can range from 30 days to under one year. The amount from product revenue represents amounts due from distributors in Europe, which are recorded net of reserves for trade discounts and allowances, and other incentives to the extent such amounts are payable to the customer by the Company. The Company monitors economic conditions to identify facts or circumstances that

may indicate that its receivables are at risk of collection. The Company provides reserves against accounts receivable for estimated losses, if any, that may result from a customer's inability to pay based on the composition of its accounts receivable, current economic conditions, and historical credit loss activity. Amounts determined to be uncollectible are charged or written-off against the reserve. The Company did not record any expected credit losses related to outstanding accounts receivable in 2022 and 2021.

Fair Value Measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

Level 1—Valuations based on quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly, such as quoted market prices, interest rates, and yield curves.

Level 3—Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable.

To the extent a valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair values requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The Company believes that the carrying amount reflected on the consolidated balance sheets for research and development tax incentive receivable, trade receivables, accounts payable, and accrued expenses approximate fair value due to their short-term maturities. The carrying value of the Company's outstanding notes payable approximates fair value (a Level 2 fair value measurement), reflecting interest rates currently available to the Company

Restricted cash and construction deposits

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on the Company's consolidated balance sheets. The Company has an outstanding letter of credit for $3.0 million associated with a lease and is required to hold this amount in a standalone bank account as of December 31, 2022 and 2021. The Company is also contractually required to maintain a cash collateral account associated with corporate credit cards and other leases in the amount of $1.3 million as of December 31, 2022 and 2021.

The Company includes the restricted cash balance in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the consolidated statements of cash flows. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported in the consolidated balance sheet that sum to the total of the amounts reported in the consolidated statement of cash flows (in thousands):

	As of December 31,	
	2022	2021
Cash and cash equivalents	$ 68,424	$ 55,912
Restricted cash	4,215	4,266
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 72,639	$ 60,178

Inventory

The Company began capitalizing inventory manufactured or purchased after the acquisition of Strimvelis in April 2018 and EMA approval of Libmeldy in December 2020. Inventory is stated at the lower of cost or estimated net realizable value with cost determined on a first-in, first-out basis. Inventory costs include raw materials, third-party contract manufacturing, third-party packaging services, and freight. Raw and intermediate materials that may be utilized for either research and development or commercial purposes are classified as inventory. Amounts in inventory that are used for research and development purposes are charged to research and development expense when the product enters the research and development process and can no longer be used for commercial purposes and, therefore, does not have an "alternative future use" as defined in authoritative guidance. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period and, if needed, writes down any excess and obsolete inventory to its estimated net realizable

value in the period it is identified. If they occur, such impairment charges are recorded as a component of cost of goods sold in the consolidated statements of operations and comprehensive income (loss). Inventory is included in prepaid expenses and other current assets on the consolidated balance sheets as its balance was not significant as of December 31, 2022 or 2021 (refer to Footnote 4).

Prior to the initial date that regulatory approval is received, costs related to the production of inventory are recorded as research and development expense on the Company's consolidated statements of operations and comprehensive income (loss) in the period incurred.

Intangible assets, net

Intangible assets consist of milestones associated with the Company's approved products net of accumulated amortization. The Company amortizes its intangible assets using the straight-line method over their estimated economic lives and periodically reviews for impairment. The Company has not recognized any impairment charges related to intangible assets to date.

Property and equipment

Property and equipment are recorded at cost and depreciated or amortized using the straight-line method over the following estimated useful lives.

Asset Type:	Estimated useful life
Lab equipment	5-10 years
Leasehold improvements	Shorter of lease term or estimated useful life
Furniture and fixtures	4 years
Office and computer equipment	3-5 years

Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property and equipment, are expensed as incurred. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts, and any resulting gain or loss is included in the consolidated statements of operations and other comprehensive loss.

Impairment of long-lived assets

Long-lived assets consist of property and equipment and operating lease right-of-use assets. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets or asset group may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant under performance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset or asset group to its carrying value. An impairment loss would be recognized when the estimated undiscounted future cash flows expected to result from the use of

an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value.

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities including salaries and benefits, share-based compensation, facilities costs, depreciation, third-party license fees, certain milestone payments, external costs incurred by outside vendors engaged to conduct clinical development activities and clinical trials, the purchase of in-process research and development assets, and costs incurred to develop a manufacturing process, perform analytical testing and manufacture clinical trial materials. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are recorded as prepaid expenses. Such amounts are recognized as an expense as the goods are delivered, the related services are performed, or until it is no longer expected that the goods will be delivered or the services rendered. In addition, funding from research grants is recognized as an offset to research and development expenses on the basis of costs incurred on the research program. Royalties to third parties associated with our research grants will be accrued when they become probable.

Accrued external research and development expenses

The Company has entered into various research and development contracts. These agreements are cancelable, and related costs are recorded as research and development expenses as incurred. When billing terms under these contracts do not coincide with the timing of when the work is performed, the Company is required to make estimates of outstanding obligations to those third parties. Any accrual estimates are based on a number of factors, including the Company's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. Actual results could differ from the estimates made by the Company. The historical accrual estimates made by the Company have not been materially different from the actual costs.

Share-based compensation

The Company measures all stock options and other stock-based awards granted based on the fair value of the award on the date of the grant and recognizes stock-based compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. The Company has elected to recognize forfeitures as they occur. Therefore, the reversal of compensation cost previously recognized for an award that is forfeited because of a failure to satisfy a service or performance condition is recognized in the period of the forfeiture. The Company classifies stock-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipients' service payments are classified.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option pricing model, which requires inputs based on certain subjective assumptions, including the fair value of the Company's common stock, expected stock price volatility, the expected term of the stock option, the risk-free interest rate for a period that approximates the expected term of the stock option, and the Company's expected dividend yield. The risk-free interest rate is based on a U.S. treasury instrument whose term is consistent with the expected term of the stock options. The expected term of the Company's options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including those in the early stages of product development with a similar and therapeutic focus. For these analyses, the Company selects companies with comparable characteristics to its own including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected term of the options/ The closing sale price per share of the Company's common stock as reported on The Nasdaq Global Market on the date of grant is used to determine the fair value, which is then used to establish the exercise price per share of share-based awards to purchase common stock.

Comprehensive loss

Comprehensive loss is composed of net loss and other comprehensive income (loss). Other comprehensive income (loss) consists of unrealized gains and losses on marketable securities and foreign currency translation gains and losses.

Leases

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on specific facts and circumstances, the existence of an identified asset(s), if any, and the Company's control over the use of the identified asset(s), if applicable. Operating lease assets represent a right to use an underlying asset for the lease term and operating lease liabilities represent an obligation to make lease payments arising from the lease. Operating lease liabilities with a term greater than one year and their corresponding right-of-use assets are recognized on the balance sheet at the commencement date of the lease based on the present value of lease payments over the expected lease term. The Company recognizes a corresponding right-of-use ("ROU") asset, initially measured as the amount of lease liability, adjusted for any initial lease costs or lease payments made before or at the commencement of the lease, and reduced by any lease incentives. The Company made an accounting policy election to not record a right-of-use asset or lease liability for leases with a term of one year or less. To date, the Company has not identified any material short-term leases, either individually or in the aggregate.

The lease liability is measured at the present value of future lease payments, discounted using the discount rate as of the lease commencement date. Future lease payments may include payments that depend on an index or a rate (such as the consumer price index or other market index). The Company initially measures payments based on an index or rate by using the applicable rate at lease commencement and subsequent changes in such rates are recognized as variable lease costs. Variable payments that do not depend on a rate or index are not included in the lease liability and are recognized as they are incurred. The Company's contracts typically do not have variable payments based on index or rate.

When readily determinable, the discount rate used to calculate the lease liability is the rate implicit in the lease. As the Company's leases do not typically provide an implicit rate, the Company utilizes an incremental borrowing rate, which is the rate incurred to borrow an amount on a collateralized basis over a similar term as the associated lease in a similar economic environment. The Company estimated the incremental borrowing rate based on the Company's currently outstanding credit facility as inputs to the analysis to calculate a spread, adjusted for factors that reflect the profile of secured borrowing over the expected term of the lease. The lease term used to calculate the lease liability includes options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. With limited exceptions, the nature of the Company's facility leases is such that there are no economic or other conditions that would indicate that it is reasonably certain at lease commencement that the Company will exercise options to extend the term.

The components of a lease should be split into three categories: lease components (e.g., land, building, etc.), non-lease components (e.g., common area maintenance, utilities, performance of manufacturing services, purchase of inventory, etc.), and non-components (e.g., property taxes, insurance, etc.). Then the fixed contract consideration (including any related to non-components) must be allocated based on fair values to the lease components and non-lease components. Although separation of lease and non-lease components is required, certain accounting policy elections are available to entities. Entities can elect accounting policies that would not separate lease and non-lease components. Rather, they would account for each lease component and the related non-lease component together as a single component. The Company has elected not to apply the accounting policy with respect to its lease of manufacturing space at a contract manufacturing organization, and as a result, the Company has allocated the consideration between the lease and non-lease components of the contract based on the respective fair values of the lease and non-lease components. The Company calculated the fair value of the lease and non-lease components using financial information readily available as part of its master services arrangement and other representative data indicative of fair value.

The Company's leases consist of only operating leases. Operating leases are recognized on the balance sheet as ROU assets, operating lease liabilities, and operating lease liabilities non-current. Fixed payments are included in the calculation of the lease balances while certain variable costs paid for certain operating and pass-through costs are excluded. Lease expense is recognized over the expected lease term on a straight-line basis.

The Company accounts for sublease income on a straight-line basis over the respective lease period and records an unbilled rent receivable for sublease income incurred but not yet paid. The Company periodically performs a collectability assessment associated with any unbilled rent receivables. The Company recognizes the sublease income as a reduction to the related operating expense associated with the head lease.

Strimvelis loss provision

As part of the GSK transaction, the Company is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company initially recorded a liability associated with the loss contract of $18.4 million in 2018. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with the Strimvelis program and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a reduction to research and development expense. The Company

has made an estimate of the expected future losses associated with Strimvelis and will adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for updated future losses.

The following table below outlines the changes to the Strimvelis loss provision for the periods ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,	
	2022	2021
Balance at beginning of period	$ 3,419	$ 4,482
Amortization of loss provision	(274)	(1,037)
Foreign currency translation	(326)	(26)
Balance at end of period	$ 2,819	$ 3,419

As of December 31, 2022, the entire balance of the Strimvelis loss provision was categorized as current. As of December 31, 2021, $0.7 million of the loss provision was classified as current, and $2.7 million was classified as non-current.

United Kingdom Research and development income tax credits

As the Company carries out research and development activities, it is able to submit tax credit claims from two UK research and development tax relief programs: the Small and Medium-Sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure Credit ("RDEC"), depending on eligibility. Qualifying expenditures largely comprise employment costs for research staff, consumables, and certain internal overhead costs incurred as part of research projects for which the Company does not receive income.

The RDEC and SME credits are not dependent on the Company generating future taxable income or on the ongoing tax status or tax position of the Company. Each reporting period, the Company assesses its research and development activities and expenditures to determine whether the nature of these costs will qualify for credit under the tax relief programs and whether the claims will ultimately be realized based on the allowable reimbursable expense criteria established by the UK government. The Company expects a proportion of expenditures incurred in relation to its pipeline research, clinical trials management, and manufacturing development activities to be eligible for the research and development tax relief programs for the year ended December 31, 2022. The Company has qualified under the more favorable SME regime for the year ended December 31, 2021 and expects to qualify under the SME regime for the year ending December 31, 2022.

The Company recognizes credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expenses. The following table outlines the changes to the research and development tax credit receivable, including amount recognized as an offset to research and development expense during the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,	
	2022	2021
Balance at beginning of period	$ 30,723	$ 17,344
Recognition of credit claims as offset to research and development expense	8,243	13,920
Receipt of credit claims	(30,811)	-
Foreign currency translation	(2,213)	(541)
Balance at end of period	$ 5,942	$ 30,723

As of December 31, 2022 and 2021, the Company's tax credit receivable was classified as current with receipt of the credit expected within twelve months of the balance sheet date.

Income taxes

The Company is primarily subject to corporation taxes in the United Kingdom, the United States, and certain European Union countries in which it has legal subsidiaries. The calculation of the Company's tax provision involves the application of country applicable tax law and requires judgment and estimates.

The Company accounts for income taxes in accordance with ASC Topic 740, *Accounting for Income Taxes*, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. The Company determines its deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and

liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the net deferred tax assets will not be realized.

The Company accounts for uncertainty in income taxes by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not-to be sustained, the tax position is then assessed as the amount of benefit to recognize in the consolidated financial statements. The amount of benefits that may be used is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate, as well as the related net interest and penalties.

Product revenue, net

Libmeldy

In January 2022, the Company began generating product revenue from sales of Libmeldy in Europe following the approval of Libmeldy by the European Commission in December 2020 for the treatment of early onset MLD, characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

The Company recognizes revenue when control of promised goods is transferred to a customer at an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods. Control of the product transfers upon infusion of the product.

To determine revenue recognition, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the Company satisfies the performance obligations. The Company only applies the five-step model to contracts when collectability of the consideration to which it is entitled in exchange for the goods the Company transfers to the customer is determined to be probable.

In certain regions of Europe and the Middle East, the Company utilizes distributors to act in an agent capacity including for patient identification and other related functions. The Company is exclusively responsible for product fulfillment and retains inventory risk and pricing discretion of the product. Evaluation of these key indicators supports the assertion that the Company maintains control over the product prior to delivery to the patient. The Company has concluded that it is the principal in these transactions and records the associated revenue on a gross basis with any payments to these entities being recorded as a selling expense.

Amounts are recorded as accounts receivable when the right to the consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. The Company expenses incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that would have been recognized is one year or less or the amount is immaterial. As of December 31, 2022, the Company has not capitalized any costs to obtain contracts.

The Company recognizes product revenue, net of variable consideration related to certain allowances and accruals, when the customer takes control of the product, which is at a point in time once the patient has been infused. Product revenue is recorded at the net sales price, or transaction price. The Company records estimated product revenue reserves, which are classified as a reduction in product revenue, to account for the components of variable consideration. Variable consideration includes the following components: government rebates, including performance-based rebates, trade discounts and allowances, and other incentives, which are described below.

These reserves are based on estimates of the amounts earned or to be claimed on the related sales and are classified as a liability. The Company's estimates of reserves established for variable consideration are calculated based upon an application of the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts. These estimates reflect the Company's historical experience, current contractual and statutory requirements, specific known market events and trends, industry data, and current expectations around final pricing. The amount of variable consideration that is included in the transaction price may be subject to constraint and is included in net product revenue only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. The actual amounts of consideration received may ultimately differ from the Company's estimates. If actual results vary, the Company adjusts these estimates, which could have an effect on earnings in the period of adjustment. The following is a summary of the types of variable consideration the Company records:

Government rebates: The Company is subject to statutory government rebates on sales in certain European countries as well as estimated rebates in certain European countries because final pricing has not yet been negotiated. The Company records reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of product revenue and a current liability that is included in accrued expenses on the Company's consolidated balance sheet. The Company is also subject to potential rebates in connection with performance criteria agreed upon with certain payors. The estimate for rebates is based on statutory discount rates, industry pricing data, current expectations around final pricing to be obtained, and historical experience of the performance of the Company's products during clinical trials. The Company classifies rebates within accrued expenses in the accompanying consolidated balance sheets.

Trade discounts and allowances: The Company may offer customers discounts, such as prompt pay discounts to remit payment in accordance with the stated terms of the invoice. These discounts are explicitly stated in the contracts and recorded in the period the related product revenue is recognized. The Company estimates which customers will earn these discounts and fees and deducts these discounts and fees in full from gross product revenue and accounts receivable at the time the Company recognizes the related revenue. The Company classifies trade discounts and allowances as a reduction of accounts receivable within the accompanying consolidated balance sheets.

Product returns: Based on the timing of revenue recognition upon treatment with the patient, the Company does not expect any returns of the Company's products.

Other incentives: While the Company does not currently have any other incentives that have been recorded to date, the Company may enter into future arrangements that have other incentives that will be recorded as a reduction of revenue.

Strimvelis

The Company's product sales of Strimvelis are currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. The hospital will purchase and pay for the products and submit a claim to the payer. The Company's contracted sales with the hospital contains a single performance obligation and the Company recognizes revenue from product sales when the Company has satisfied its performance obligation, which is upon transferring control of the products to the hospital. The Company evaluated the variable consideration under ASC 606 and there is currently no variable consideration included in the transaction price for the products. Costs to manufacture and deliver the product and those associated with administering the therapy are included in the cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates there is limited risk of product return, including the risk of product expiration.

Collaboration revenue

The terms of the Company's collaboration agreements may include consideration such as non-refundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services, sales-based milestones and royalties on product sales.

The Company first evaluates collaboration arrangements to determine whether the arrangement (or part of the arrangement) represents a collaborative arrangement pursuant to ASC Topic 808, *Collaborative Arrangements*, based on the risks and rewards and activities of the parties pursuant to the contractual arrangement. The Company accounts for any collaborative arrangement or elements within the contract that are deemed to be a collaborative arrangement, and not a customer relationship, in accordance with ASC 808. Through December 31, 2022, the Company entered into one agreement with Pharming Group N.V. (the "Pharming Agreement", see Note 16) that is accounted for pursuant to ASC 606 five-step model.

The Company recognizes the transaction price allocated to upfront license payments as revenue upon delivery of the license to the customer and resulting ability of the customer to use and benefit from the license, if the license is determined to be distinct from the other performance obligations identified in the contract. If the license is considered to not be distinct from other performance obligations, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied (i) at a point in time, but only for licenses determined to be distinct from other performance obligations in the contract, or (ii) over time, and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from license payments. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

The Pharming Agreement entitles the Company to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, regulatory milestones, and sales-based milestones. The Company is also eligible to receive from Pharming tiered royalty payments on worldwide net sales. The Company evaluates whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the

transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within the Company's control, are considered constrained until such approval is received. Upfront and ongoing development milestones per the collaboration agreements are not subject to refund if the development activities are not successful. At the end of each subsequent reporting period, the Company re-evaluates the probability of a significant reversal of the cumulative revenue recognized for the milestones, and, if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators in the period of adjustment.

The Company may enter into an agreement that includes sales-based milestone payments and royalties in exchange for a license of intellectual property. The Company considers the underlying facts and circumstances of these agreements, noting whether the future payments are contingent upon future sales and whether they are dependent on a third party's ability to successfully commercialize a product using the licensed intellectual property. The Company also considers whether the license is the only, or predominant, item to which the milestone payments and royalties relate. If the Company concludes the license is the predominant item in the agreement, therefore the primary driver of value, the Company excludes sales-based milestone payments and royalties from the transaction price until the sale occurs (or, if later, until the underlying performance obligation to which some or all of the royalty has been allocated has been satisfied or partially satisfied). Currently, the Company has not recognized any royalty revenue resulting from the Pharming Agreement.

ASC 606 requires the Company to allocate the arrangement consideration on a relative standalone selling price basis for each performance obligation after determining the transaction price of the contract and identifying the performance obligations to which that amount should be allocated. The relative standalone selling price is defined in ASC 606 as the price at which an entity would sell a promised good or service separately to a customer. If other observable transactions in which the Company has sold the same performance obligation separately are not available, the Company is required to estimate the standalone selling price of each performance obligation. Key assumptions to determine the standalone selling price may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

Whenever the Company determines that a contract should be accounted for as a combined performance obligation, which is recognized over time, it will utilize the cost-to-cost input method. Revenue will be recognized over time using the cost-to-cost input method, based on the total estimated costs to fulfill the obligations. The Company will recognize revenue as services are delivered. Significant management judgment is required in determining the estimate of total costs required under an arrangement and the period over which the Company is expected to complete its performance obligations under an arrangement.

Consideration that does not meet the requirements to satisfy the above revenue recognition criteria is a contract liability and is recorded as deferred revenue in the consolidated balance sheets. Short-term deferred revenue consists of amounts that are expected to be recognized as revenue in the next 12 months. Amounts that the Company expects will not be recognized within the next 12 months are classified as long-term deferred revenue.

The Company recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time. In particular, for the Company's collaborations with Pharming, revenue attributable to research services is recognized as those services are provided, based on the costs incurred to date.

Net loss per share

Basic net loss per share is computed by dividing the net loss by the weighted average number of ordinary shares outstanding for the period. Diluted net loss is computed by adjusting net loss based on the potential impact of dilutive securities. Diluted net loss per share is computed by dividing the diluted net loss by the weighted average number of ordinary shares outstanding for the period, including potentially dilutive ordinary shares. For the purpose of this calculation, outstanding options and unvested restricted shares are considered potential dilutive ordinary shares. Since the Company was in a loss position for all periods presented, the basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all potential ordinary share equivalents outstanding would have been anti-dilutive.

The following securities, presented based on amounts outstanding at each period end, are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti-dilutive:

	As of December 31,	
	2022	2021
Share options	13,076,959	14,042,781
Unvested restricted incentive shares	2,253,199	512,908
	15,330,158	14,555,689

Recent accounting pronouncements

In November 2021, the FASB issued ASU No. 2021-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance*, which requires increased transparency in the disclosures about government assistance in the notes to the financial statements. This ASU is effective for the Company beginning January 1, 2022, and interim periods within that year, with early adoption permitted. The Company adopted and applied the amendments of this ASU to its disclosures. The application of this ASU did not have a material impact on the Company's financial position, results of operations or cash flows.

In March 2020, the FASB issued ASU 2020-04, Reference Rate Reform (Topic 848)*: Facilitation of the Effects of Reference Rate Reform on Financial Reporting* and issued two subsequent amendments: ASU 2021-01, issued in January 2021, refines the scope of ASU and clarifies some of its guidance as part of the FASB's monitoring of global reference rate reform activities and ASU 2022-06, issued in December 2022, which extends the effective period of the ASU through December 31, 2023 (collectively, including ASU 2020-04, "ASC 848"). ASC 848 provides temporary optional expedients and exceptions to the GAAP guidance on contract modifications and hedge accounting to ease the financial reporting burdens related to the expected market transition from the London Interbank Offered Rate ("LIBOR") and other interbank offered rates to alternative reference rates. ASC 848 is effective for all entities as of March 12, 2020, through December 31, 2023, at which time transition is expected to be complete. The Company is currently reviewing the provisions of this pronouncement, specifically its impact on its notes payable, but does not expect this guidance will have a material impact on the Company's consolidated financial statements.

3. Fair Value Measurements and Marketable Securities

The following tables present information about the Company's financial assets that have been measured at fair value as of December 31, 2022 and 2021, and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

	Fair Value Measurements as of December 31, 2022			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 1,239	$ —	$ —	$ 1,239
U.S. treasuries	—	6,600	—	6,600
U.S. government securities	—	5,200	—	5,200
Commercial paper	—	14,122	—	14,122
Total cash equivalents	$ 1,239	$ 25,922	$ —	$ 27,161
Marketable securities				
U.S. government securities	$ —	$ 1,984	$ —	$ 1,984
Corporate bonds	—	25,475	—	25,475
Commercial paper	—	47,867	—	47,867
Total marketable securities	$ —	$ 75,326	$ —	$ 75,326
Total Assets	$ 1,239	$ 101,248	$ —	$ 102,487

	Fair Value Measurements as of December 31, 2021			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 21,085	$ —	$ —	$ 21,085
U.S. government securities	—	7,321	—	7,321
Commercial paper	—	13,198	—	13,198
Total cash equivalents	$ 21,085	$ 20,519	$ —	$ 41,604
Marketable securities				
Corporate bonds	$ —	$ 94,794	$ —	$ 94,794
Commercial paper	—	69,401	—	69,401
Total marketable securities	$ —	$ 164,195	$ —	$ 164,195
Total	$ 21,085	$ 184,714	$ —	$ 205,799

The Company classifies its money market funds as Level 1 assets since it measures fair value using quoted prices in active markets for identical assets. The Level 2 assets include commercial paper, U.S. government securities, U.S. treasuries, and corporate bonds and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data. The Company did not hold any Level 3 assets during the periods presented.

The Company evaluates transfers between levels at the end of each reporting period. There were no transfers between Level 1 and Level 2 assets during the periods presented.

Marketable Securities

The following tables summarize the amortized cost and fair value of the Company's available-for-sale marketable debt securities (in thousands):

	December 31, 2022				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
U.S. government securities	$ 7,188	$ 1	$ (6)	$ —	$ 7,183
U.S. treasuries	6,599	1	—	—	6,600
Corporate bonds	25,656	—	(180)	—	25,476
Commercial paper	62,038	3	(52)	—	61,989
Total	$ 101,481	$ 5	$ (238)	$ —	$ 101,248

	December 31, 2021				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
Corporate bonds	$ 102,224	$ —	$ (109)	$ —	$ 102,115
Commercial paper	82,657	—	(58)	—	82,599
Total	$ 184,881	$ —	$ (167)	$ —	$ 184,714

The following table summarizes the Company’s available-for-sale marketable debt securities by contractual maturity, as of December 31, 2022 and 2021 (in thousands):

	2022	2021
Maturities in one year or less	$ 98,277	$ 172,575
Maturities between one and three years	2,971	12,139
Total	$ 101,248	$ 184,714

All investments in an unrealized loss position were in this position for less than 12 months. The Company evaluated its securities for potential other-than-temporary impairment and considered the decline in market value to be primarily attributable to current economic and market conditions. Additionally, the Company does not intend to sell the securities in an unrealized loss position and does not expect it will be required to sell the securities before recovery of the unamortized cost basis. Given the Company's intent and ability to hold such securities until recovery, and the lack of a significant change in credit risk for these investments, the Company does not consider these investments to be impaired as of December 31, 2022.

There were no realized gains or losses recognized on investments for the years ended December 31, 2022 and 2021.

4. Prepaid expenses and other current assets

Prepaid expenses and other current assets consist of the following (in thousands):

	December 31,	
	2022	2021
Prepaid external research and development expenses	$ 881	$ 2,438
Inventories	3,400	2,016
Other prepayments	1,817	6,128
VAT receivable	1,077	1,169
Construction deposit - current	—	7,909
Non-trade receivables	1,851	3,351
Rent deposits	960	—
Total prepaid expenses and other current assets	$ 9,986	$ 23,011

5. Property and equipment

Property and equipment consist of the following (in thousands):

	December 31,	
	2022	2021
Property and equipment:		
Lab equipment	$ 6,722	$ 5,937
Leasehold improvements	5,069	2,450
Furniture and fixtures	226	303
Office and computer equipment	2,153	2,023
Construction-in-progress	759	211
Property and equipment	14,929	10,924
Less: accumulated depreciation	(6,791)	(6,157)
Property and equipment, net	$ 8,138	$ 4,767

Depreciation expense for the years ended December 31, 2022 and 2021 was $2.4 million and $2.2 million, respectively.

6. Intangible assets, net

Intangible assets, net of accumulated amortization, consisted of the following (in thousands):

	As of December 31, 2022		
	Cost	Accumulated Amortization	Net
License milestones	$ 4,069	$ (509)	$ 3,560
Total	$ 4,069	$ (509)	$ 3,560

	As of December 31, 2021		
	Cost	Accumulated Amortization	Net
License milestones	$ 4,329	$ (180)	4,149
Total	$ 4,329	$ (180)	$ 4,149

License intangibles consist of capitalized milestone payments or accruals of payments the Company has deemed probable upon receiving regulatory approval of Libmeldy in the EU. The license intangibles are being amortized on a straight-line basis over the remaining useful life of the related patents of approximately twelve years. Amortization of intangible assets was $0.3 million and $0.2 million for the years ended December 31, 2022 and 2021, respectively. The effect of foreign currency translation on the net carrying value of intangible assets during the year ended December 31, 2022 was $0.2 million. The effect of foreign currency translation on the net carrying value of intangible assets during 2021 was not material.

The following table summarizes the estimated future amortization for intangible assets for the next five years and thereafter (in thousands):

2023	$ 343
2024	343
2025	343
2026	343
2027	343
Thereafter	1,845
Total	$ 3,560

7. Other assets

Other assets consist of the following (in thousands):

	December 31,	
	2022	2021
Deferred tax assets	$ 7,369	$ 4,086
Deposits	1,048	1,404
Deferred financing costs	462	693
Other non-current assets	3,196	3,407
Total other assets	$ 12,075	$ 9,590

8. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31,	
	2022	2021
Accrued external research and development expenses	$ 11,230	$ 9,273
Accrued payroll and related expenses	12,312	8,521
Accrued milestone payments	85	2,058
Accrued professional fees	2,263	854
Accrued other	2,562	2,941
Accrued governmental rebates	2,300	—
Strimvelis liability - current portion	3,685	671
Total accrued expenses and other current liabilities	$ 34,437	$ 24,318

9. Restructuring charges

On March 30, 2022, the Company announced its commitment to focus on severe neurometabolic diseases and early research programs, and to discontinue its investment in and seek strategic alternatives for the Company's programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich syndrome ("WAS"), OTL-102 for treatment of X-linked chronic granulomatous disease ("X-CGD"), and Strimvelis for adenosine deaminase severe combined immunodeficiency ("ADA-SCID"). During the year ended December 31, 2022, the Company recognized a one-time charge during of approximately $1.7 million, which relates to employee-related termination costs, of which $1.4 million and $0.3 million was recognized in research and development expenses and selling, general, and administrative expenses, respectively, in the Company's consolidated statements of operations and comprehensive loss. Activity during the year ended December 31, 2022, was as follows (in thousands):

	Year Ended December 31,
	2022
Balance at beginning of period	$ 6
Charged to expense	2,481
Non-cash adjustments and foreign currency translation	(760)
Payments made	(1,727)
Balance at end of period	$ -

There were no restructuring costs incurred during the year ended December 31, 2021.

10. Leases

Operating leases- office and lab space

In January 2018, December 2018, and February 2022 the Company entered into lease agreements for office space in London, United Kingdom. The leases entered into in 2018 both terminate in January 2023 and there were no options to extend the lease term. The lease entered into in March 2022 expires in February 2032 and there are no options to extend the lease term. The combined annual rental payments, including variable payments, under the lease agreements were $1.7 million in 2022 and $1.8 million in 2021. The Company also rented lab spaces in London in 2021, for which it made $0.2 million in payments in 2022 and 2021.

In March 2018, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which terminated in September 2022. The annual rental payments, including variable payments, were $0.3 million in 2022 and $0.4 million in 2021. The Company subleased the space starting in August 2021, and recognized $0.2 and $0.1 million in sublease income in 2022 and 2021, respectively.

In July 2019, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which commenced in January 2020. The lease terminates in September 2026 and has no options for term extension. The annual rental payments, including variable payments, were $1.2 million and $1.1 million in 2022 and 2021, respectively. The lease agreement includes annual rent escalation provisions.

As of December 31, 2022, the carrying value of the operating lease right-of-use assets in Boston and London was $8.1 million and the lease liabilities was $8.7 million. As of December 31, 2021, the carrying value of the operating lease right-of-use assets in Boston and London was $4.1 million and the lease liabilities was $4.3 million.

Fremont operating lease and sublease agreements

In December 2018, the Company leased manufacturing, laboratory, and office space in Fremont, California (the “Fremont facility” and the “Head Lease”) which terminates in May 2030. In May 2020, the Company committed to a restructuring plan whereby it ceased construction and build-out of the Fremont facility. In December 2020, the Company entered into a sublease agreement (the “Sublease”) with an unrelated third-party (the “subtenant”) whereby the Company subleased the entire Fremont facility to the subtenant. The Company accounts for the Head Lease and Sublease as two separate contracts. Both the Head Lease and Sublease were determined to be operating leases.

The Head Lease annual rental payments, including variable payments, were $3.2 million in 2022 and $3.1 million in 2021. The Head Lease includes annual rent escalation provisions. The Company was provided with 8 months of free rent. Subject to the terms of the Head Lease agreement, the Company executed a $3.0 million letter of credit upon signing the lease, which may be reduced by 25% subject to reduction requirements specified therein. This amount is classified as restricted cash on the consolidated balance sheets.

As of December 31, 2022, the carrying value of the Fremont Head Lease right-of-use asset was $8.8 million and the lease liability was $12.0 million. The Head Lease provides for up to $5.3 million in tenant improvement allowances to be reimbursed to the Company by the landlord. These tenant improvement allowances have been included in the calculation of the operating lease liability and are currently expected to be received in 2023. The Company continues to assess the expected receipt of the tenant improvement allowances and may remeasure the right-of-use asset and liability from time to time as facts and circumstances may change.

The Sublease commenced in December 2020 and is in force for the remainder of the Head Lease term. The Sublease provided for 12 months of free rent until December 2021. The sublease provides for cash base rent payments with an annual rent escalation provision. The subtenant is also responsible for paying all operating expenses associated with the Head Lease. The Sublease also includes pass-through of up to $5.3 million in tenant improvement allowances to the subtenant, subject to the Company being reimbursed for the allowances per the terms of the Head Lease. The Subtenant provided the Company with a $2.6 million security deposit, which may be converted to a letter of credit upon providing evidence of $2.6 million in construction expenditures. The Company accounts for the security deposit within other long-term liabilities.

Embedded operating lease arrangement

In July 2020, the Company entered into a manufacturing and technology development master agreement for research and development and commercial production with AGC Biologics, S.p.A. (formerly MolMed S.p.A.) (“AGC”) pursuant to which AGC will develop, manufacture and supply certain viral vectors and conduct cell processing activities for certain Company development and commercial programs ("AGC Agreement").

The Company determined that the AGC Agreement contains an embedded lease as it includes a provision for manufacturing suites designated for the Company's exclusive use during the term of the agreement. The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The agreement may be extended for an additional two years by mutual agreement of the Company and AGC. The Company does not deem it probable that it will exercise the option to extend as of December 31, 2022. The Company paid $2.5 million and $3.1 million in rental payments in 2022 and 2021, respectively. As of December 31, 2022, the carrying value of the embedded operating lease right-of-use asset was $5.8 million and the lease liability was $5.3 million. As of December 31, 2021, the carrying value of the embedded operating lease right-of-use asset was $10.7 million and the lease liability was $9.3 million.

Summary of all lease costs recognized under ASC 842

Our facility leases described above generally contain customary provisions allowing the landlords to terminate the leases if we fail to remedy a breach of any of our obligations under any such lease within specified time periods, or upon our bankruptcy or insolvency. The leases do not include any restrictions or covenants that had to be accounted for under the lease guidance. The following table contains a summary of the lease-related costs recognized within operating expenses, and other information pertaining to the Company's operating leases as of December 31, 2022 and 2021 (in thousands, where applicable):

	2022	2021
Fixed lease cost	$ 7,693	$ 7,701
Variable lease cost	1,602	1,696
Sublease income	(2,820)	(2,746)
Total lease cost	$ 6,475	$ 6,651
Other information		
Operating cash flows used for operating leases	$ 7,442	$ 7,989
Weighted-average remaining lease term (years)	6.5	6.0
Weighted-average discount rate	8.5%	8.7%

Fixed lease cost represents the ASC 842 rent expense associated with the amortization of our right-of-use assets and lease liabilities. Variable lease cost are the amounts owed by the Company to a lessor that are not fixed, such as reimbursement for common area maintenance and utilities costs and are not included in the calculation of the Company's operating lease right of use assets or operating lease liabilities and are expensed when incurred. Sublease income represents the straight-line recognition of base rent sublease income over the term of the Sublease, and recognition of pass-through operating expense costs per the terms of the Sublease.

During the year ended December 31, 2022, the Company obtained right of use assets valued at $6.1 million in exchange for lease liabilities of $6.1 million. During the year ended December 31, 2021, the Company obtained $0.6 million in right of use assets in exchange for $0.6 million in lease liabilities.

As of December 31, 2022, future minimum base rent commitments under ASC 842 under the Company's property leases were as follows (in thousands):

Due in:	Gross lease payments	Gross sublease receipts	Net lease payments
2023	$ 6,517	$ (2,246)	$ 4,271
2024	6,972	(2,313)	4,659
2025	6,035	(2,382)	3,653
2026	4,809	(2,454)	2,355
2027	3,774	(2,527)	1,247
Thereafter	12,266	(6,432)	5,834
Total future minimum lease payments	$ 40,373	$ (18,354)	$ 22,019
Less: imputed interest	(14,703)		
Total operating lease payments	$ 25,670		

11. Notes payable

In May 2019, the Company entered into a senior term facilities agreement, which was amended in April 2020 (the "Original Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), as agent, and additional lenders from time to time (together with MidCap Financial, the "Lenders"), to borrow up to $75.0 million in term loans.

In May 2021, the Company amended and restated the Original Credit Facility (the "Amended Credit Facility"). Under the Amended Credit Facility, the Lenders agreed to make term loans available to the Company in the aggregate amount of $100.0 million, including increasing the principal on the initial term loan to $33.0 million, from $25.0 million. To date, the Company has borrowed $33.0 million under the amended initial term loan. The remaining $67.0 million under the Amended Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a $33.0 million term loan available no earlier than July 1, 2022 and no later than July 1, 2023 upon certain regulatory approvals and evidence of the Company having $100 million in cash and cash equivalent investments; and the third term loan being a $34.0 million term loan available no earlier than July 1, 2023 and no later than July 1, 2024 upon evidence of the Company having $100 million in cash and cash equivalent investments and attaining a pre-specified trailing 12-month revenue target.

Each term loan under the Amended Credit Facility bears interest at an annual rate equal to 5.95% plus LIBOR. The Company is required to make interest-only payments on the term loan for 18 months following the date of the Amended Credit Facility, unless the Company is eligible for the second tranche, in which case the Company may elect to make interest-only payments for 30 months following the date of the Amended Credit Facility. The term loans under to the Amended Credit Facility begin amortizing on either the 18-month or the 30-month anniversary of the Amended Credit Facility (as applicable), with equal monthly payments of principal plus interest to be made by the Company to the Lenders in consecutive monthly installments until the loan maturity date. In addition, a final payment of 3.5% is due on the loan maturity date. The Company is accruing the final payment amount of $1.2 million associated with the first term loan of the Amended Credit Facility, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the loan maturity date.

The Amended Credit Facility includes affirmative and negative covenants. The affirmative covenants include, among others, covenants requiring the Company to maintain their legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage, maintain property, pay taxes, satisfy certain requirements regarding accounts and comply with laws and regulations. The negative covenants include, among others, restrictions on the Company transferring collateral, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, making investments, creating liens, amending material agreements and organizational documents, selling assets, changing the nature of the business and undergoing a change in control, in some cases subject to certain exceptions. The Company is also subject to an ongoing minimum cash financial covenant in which the Company must maintain unrestricted cash in an amount not less than $20.0 million following the utilization of the second term loan and not less than $35.0 million following the utilization of the third term loan.

In January 2023, the Company again amended and restated the credit facility to change from LIBOR to SOFR. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

Notes payable consisted of the following (in thousands):

	December 31,	
	2022	2021
Notes payable, net of issuance costs	$ 31,970	$ 32,669
Less: current portion	(9,429)	(786)
Notes payable, net of current portion	22,541	31,883
Accretion related to final payment	450	203
Notes payable, long term	$ 22,991	$ 32,086

As of December 31, 2022, the future principal payments and final payment that are due are as follows (in thousands):

	Aggregate Minimum Payments
2023	$ 9,429
2024	9,429
2025	9,429
2026	5,084
Total	33,371
Less current portion	(9,429)
Less unamortized portion of final payment	(705)
Less unamortized debt issuance costs	(246)
Notes payable, long term	$ 22,991

During the years ended December 31, 2022 and 2021, the Company recognized $3.0 million and $2.5 million of interest expense related to the term loan, respectively. The effective annual interest rate as of December 31, 2022 and 2021, on the outstanding debt under the Term Loan was approximately 9.2% and 8.4%, respectively.

12. Share-based compensation

The Company maintains four equity compensation plans; the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"), the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "2018 Plan"), the 2018 Employee Share Purchase Plan (the "ESPP"), and the 2020 Inducement Equity Plan (the "Inducement Plan"). The board of directors has determined not to make any further awards under the 2016 plan. As of December 31, 2022, there were 5,341,768 shares available for grant under the 2018 Plan, 721,500 available for grant under the Inducement Plan, and 627,677 shares available for grant under the ESPP.

The numbers of options and restricted stock units, the weighted average grant date fair values per stock option and per share, and the weighted average exercise prices are all shown below on a per ordinary share basis. Effective March 10, 2023, The Company's ADSs that are listed on the NASDAQ Capital Market each represent ten ordinary shares.

On October 4, 2022, the Company's Compensation Committee approved a one-time stock option repricing for certain previously granted and still outstanding options held by the Company's employees and certain independent contractors which had an exercise price above $1.25. As a result of the repricing, the exercise price for 7,946,139 vested and unvested options outstanding was lowered to $0.58. No other terms of the repriced options were modified and the repriced stock will continue to vest according to their original vesting schedules and will retain their original expiration dates. The repricing resulted in one-time stock-based compensation expense of $0.9 million related to vested options and incremental stock option expense of $0.8 million related to unvested options which will be amortized on a straight-line basis over the remaining vesting period of those options.

Share options

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option-pricing model using the range of assumptions for the years ended December 31, 2022 and 2021, as noted in the following table:

	Year Ended December 31,	
	2022	2021
Risk-free interest rate	1.5% - 4.4%	0.5% - 1.3%
Expected term (in years)	2.0 - 6.1	5.3 - 6.1
Expected volatility	74.4% - 79.5%	74.2% - 78.7%
Expected dividend rate	0.0%	0.0%

The following table summarizes option activity under the plans for the year ended December 31, 2022:

	Shares	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2021	17,300,740	$ 6.57		
Granted	4,600,154	0.56		
Exercised	(699,234)	-		
Forfeited	(4,777,493)	6.81		
Outstanding at December 31, 2022	16,424,167	$ 1.56	7.38	$ -
Vested and expected to vest at December 31, 2022	16,424,167	$ 1.56	7.38	$ -
Exercisable at of December 31, 2022	9,212,552	$ 2.28	6.26	$ -

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's ordinary shares for those options that had exercise prices lower than the fair value of the Company's ordinary shares. During the years ended December 31, 2022 and 2021, the total intrinsic value of share options exercised was $0.4 million and $7.4 million, respectively. The weighted average grant date fair value per share of options granted during the years ended December 31, 2022 and 2021, was $0.32 and $3.10, respectively.

Restricted share units

CEO award

The Company granted 195,000 performance based RSUs with a total grant date fair value of $1.4 million to its Chief Executive Officer, Bobby Gaspar, M.D., Ph.D., in April 2020. The award vests on January 2, 2024 as to 1/3 of the award for each of the first three to occur of four milestones, if each such milestone is achieved by the Company on or before December 31, 2023 and Dr. Gaspar remains continuously employed with the Company through January 2, 2024. The milestones relate to the achievement of specific clinical and regulatory milestones. No performance-based share unit performance conditions associated with the CEO award were deemed probable and none vested during the year ended December 31, 2022.

Time-based restricted share units

Time-based restricted share units vest in equal annual installments over a three-year period.

The following table summarizes restricted share unit award activity for the year-end December 31, 2022:

	Performance-based RSUs	Time-based RSUs	Total RSUs	Weighted Average Grant Date Fair Value per Share
Unvested at December 31, 2021	195,000	123,333	318,333	$ 6.41
Granted	—	2,192,988	2,192,988	0.46
Vested	—	(55,001)	(55,001)	5.58
Forfeited	—	(392,444)	(392,444)	0.60
Unvested at December 31, 2022	195,000	1,868,876	2,063,876	$ 0.55

During the years ended December 31, 2022 and 2021, the total fair value of time-based RSU's that vested was $0.3 million and $0.3 million, respectively.

Share-based compensation

Share-based compensation expense related to share options, restricted share unit awards, and the employee stock purchase plan was classified in the consolidated statements of operations and comprehensive loss as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Research and development	$ 6,791	$ 9,214
Selling, general and administrative	9,219	13,322
Total	$ 16,010	$ 22,536

Total share-based compensation by award type was as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Restricted share units	$ 838	$ 550
Share options	15,172	21,986
Total	$ 16,010	$ 22,536

As of December 31, 2022, total unrecognized compensation cost related to options was $14.0 million. This amount is expected to be recognized over a weighted average period of 2.34 years. As of December 31, 2022, total unrecognized compensation cost related to time-based RSUs was $0.8 million. This amount is expected to be recognized over a weighted average period of 1.96 years. As of December 31, 2022, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $1.4 million, the timing of recognition will be dependent upon achievement of milestones.

13. License and research arrangements

GSK asset purchase and license agreement

In April 2018, the Company completed an asset purchase and license agreement (the "GSK Agreement") with subsidiaries of GSK to acquire a portfolio of autologous ex vivo gene therapy assets and licenses for rare diseases and option rights on three additional programs in pre-clinical development from Telethon Foundation and San Raffaele Hospital ("Telethon-OSR"). The portfolio of programs and options acquired consisted of two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS, one earlier stage clinical gene therapy program for TDT, Strimvelis, and option rights exercisable upon completion of clinical proof of concept studies for three additional earlier-stage development programs, which option rights have all subsequently lapsed.

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations, resulting in total consideration of $133.6 million, which was recorded in the second quarter of 2018.

The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher ("PRV") from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDT, the first of which GSK retained beneficial ownership over. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As part of the GSK Agreement the Company is also required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site.

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. The Company will pay a flat mid-single digit percentage royalty on the annual net sales of Strimvelis. The Company will also pay tiered royalty rates at a percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at a percentage from the high single-digits to low double-digit for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition or through December 31, 2022, and are not included as part of consideration.

Telethon-OSR research and development collaboration and license agreements

In connection with the Company's entering into the GSK Agreement in April 2018, the Company also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous ex vivo gene therapies for ADA-SCID, WAS, MLD and TDT.

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones, up to an aggregate of approximately €31.0 million ($33.4 million at December 31, 2022). Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses of the collaboration programs.

In May 2019, the Company entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Company an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's ex vivo autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I, including the Hurler variant ("MPS-IH"). Under the terms of the agreement, Telethon-OSR received €15.0 million ($16.1 million at December 31, 2022) in upfront and milestone payments from the Company upon entering into the agreement, resulting in $17.2 million in in-process research and development expense. The Company is also required to pay up to €28.0 million ($30.1 million at December 31, 2022) related to milestone payments contingent upon achievement of certain development, regulatory and commercial milestones. Additionally, the Company will be required to pay Telethon a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

UCLB/UCLA license agreement

In February 2016, and amended in July 2017, the Company completed the UCLB/UCLA license agreement, under which the Company has been granted exclusive and non-exclusive, sublicensable licenses under certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories.

In exchange for these rights, in 2016, the Company made upfront cash payments consisting of $0.8 million for the license to the joint UCLB/UCLA technology and $1.1 million for the license to the UCLB technology and manufacturing technology. The Company also issued an aggregate of 4,665,384 ordinary shares to UCLB, of which 1,224,094, and 3,441,290 ordinary shares were issued in 2017 and 2016, respectively. The Company recorded research and development expenses based on the fair value of the ordinary shares as of the time the agreement was executed or modified.

Under the UCLB/UCLA License Agreement, the Company may become obligated to make payments to the parties of up to an aggregate of £19.9 million ($24.1 million at December 31, 2022) upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

In June 2021, the Company terminated the license to its OTL-101 program for ADA-SCID, which was granted pursuant to the UCLB/UCLA license agreement. Except for the termination of such license, the UCLB/UCLA license agreement continues in full force and effect. Unless terminated earlier by either party, the UCLB/UCLA license agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, and amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica plc whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and whereby Oxford BioMedica will provide process development services ("Oxford BioMedica Development Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Development Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and fourth milestones were achieved, and the Company issued 150,826 ordinary shares. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million which was recorded to research and development expense. No milestones were met during the year ended December 31, 2022. The Company may also pay low single-digit percentage royalties on net sales of collaborated products generated under the Oxford BioMedica Agreement.

14. Income taxes

The components of net loss before income taxes for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	December 31,	
	2022	2021
U.K.	$ (156,000)	$ (147,337)
Non-U.K.	2,966	3,581
Net loss before taxes	$ (153,034)	$ (143,756)

The provision for (benefit from) income taxes for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	December 31,	
	2022	2021
Current (benefit) provision		
Federal—United States	$ 618	$ (1,025)
State—United States	144	334
Other foreign	147	388
United Kingdom	—	—
Total current (benefit) provision	909	(303)
Deferred provision (benefit)		
Federal—United States	(3,066)	1,099
State—United States	(204)	(312)
United Kingdom	(13)	—
Other foreign	—	344
Total deferred provision (benefit)	(3,283)	1,131
Total provision (benefit) for income taxes	$ (2,374)	$ 828

The following table presents a reconciliation of income tax expense (benefit) computed at the UK statutory income tax rate to the effective income tax rate as reflected in the consolidated financial statements (in thousands):

	December 31,	
	2022	2021
Income taxes at United Kingdom statutory rate	$ (29,072)	$ (27,313)
Change in valuation allowance	34,333	59,691
Reduction in research expense for credits granted	1,805	6,674
Change in tax rates	(8,240)	(38,785)
Tax credits	(2,049)	(2,232)
U.S. Deduction for foreign derived intangible income	(1,489)	(196)
Permanent differences, including share-based compensation deduction shortfalls	2,387	2,863
U.S. state income taxes	(45)	17
Foreign rate differential	(4)	109
Total provision (benefit) for income taxes	$ (2,374)	$ 828

The Company's income tax expense for the year ended December 31, 2022, compared to the year ended December 31, 2021, decreased primarily related to an increase of the U.S. deduction for foreign derived intangible income ("FDII"), a decrease to the amount of shortfalls related to share-based compensation that is not deductible for tax purposes, and a decrease in the non-U.K. profit before tax.

During 2021, the U.K. Government announced that from April 1, 2023, the corporation tax rate would increase to 25%. This new law was enacted on June 10, 2021. The overall effect of the change was an increase in net deferred tax assets of $38.8 million and an increase in valuation allowance by an equal amount.

The Company accounts for income taxes in accordance with ASC Topic 740. Deferred income tax assets and liabilities are determined based upon temporary differences between the financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The following table presents the principal components of the Company's deferred tax assets and liabilities as of December 31, 2022 and 2021 (in thousands):

	December 31,	
	2022	2021
Deferred tax assets		
Net operating loss carryforwards	$ 158,344	$ 126,563
Amortization	11,215	25,206
Research and development credits	2,525	2,449
Capitalized research and development costs	2,285	—
Share-based compensation	9,282	9,353
Accruals	946	798
Lease liability	6,126	6,444
Property and equipment	—	1,022
Total deferred tax assets	190,723	171,835
Valuation allowance	(177,630)	(161,573)
Fixed assets and right-of-use asset	(5,724)	(6,176)
Other non-current assets (net deferred tax assets and liabilities)	$ 7,369	$ 4,086

For the years ended December 31, 2022 and 2021, the Company had cumulative U.K. net operating loss carryforwards of approximately $633.4 million and $506.2 million, respectively. U.K. losses not surrendered may be carried forward indefinitely, subject to numerous utilization criteria and restrictions and are fully offset by a valuation allowance. For the years ended December 31, 2022 and 2021, the Company also had U.S. federal orphan drug tax credits of $0.7 million and $0.6 million, respectively, and U.S. state research and development tax credits of $2.2 million and $2.4 million. The U.S. federal orphan drug tax credits expire in 2042, while the U.S. state research and development credits may be carried forward indefinitely and are offset by a valuation allowance.

In measuring the Company's deferred tax assets, the Company considers all available evidence, both positive and negative, to determine whether, based on the weight of that evidence, a valuation allowance is needed for all or some portion of the deferred tax assets. Significant judgment is required in considering the relative impact of the negative and positive evidence, and weight given to each category of evidence is commensurate with the extent to which it can be objectively verified. The more negative evidence that exists, the more positive evidence is necessary, and the more difficult it is to support a conclusion that a valuation allowance is not needed. Additionally, the Company utilizes the "more likely than not" criteria established in FASB ASC Topic 740 to determine whether the future tax benefit from the deferred tax assets should be recognized. As a result, the Company has established valuation allowances on the deferred tax assets in jurisdictions that have incurred net operating losses and in which it is more likely than not that such losses will not be utilized in the foreseeable future.

As of each reporting date, the Company considers new evidence, both positive and negative, that could impact the Company's view with regard to the future realization of our deferred tax assets. Management has considered the Company's history of cumulative net losses in the U.K., along with estimated future taxable income and has concluded that it is more likely than not that the Company will not realize the benefits of its U.K. deferred tax assets and U.S. state research and development tax credits. Accordingly, the Company has maintained a full valuation allowance against these net deferred tax assets as of December 31, 2022 and 2021, respectively.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2022 and 2021 related primarily to the increase in UK net operating loss carryforwards as follows (in thousands):

	December 31,	
	2022	2021
Valuation allowance as of beginning of year	$ (161,573)	$ (103,890)
Increases recorded to income tax provision	(34,248)	(59,691)
Effect of foreign currency translation	18,191	2,008
Valuation allowance as of end of year	$ (177,630)	$ (161,573)

The Company applies the authoritative guidance on accounting for and disclosure of uncertainty in tax positions, which requires the Company to determine whether a tax position of the Company is more likely than not to be sustained upon

examination, including resolution of any related appeals of litigation processes, based on the technical merits of the position. For tax positions meeting the more likely than not threshold, the tax amount recognized in the financial statements is reduced by the largest benefit that has a greater than fifty percent likelihood of being realized upon the ultimate settlement with the relevant taxing authority. There were no material uncertain tax positions as of December 31, 2022 and 2021.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022, and 2021, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statement of operations.

The Company and its subsidiaries file income tax returns in the UK, the U.S., and various foreign jurisdictions. Generally, the tax years 2018 through 2022 remain open to examination by the major taxing jurisdictions to which the Company is subject. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the federal, state, or foreign tax authorities, if such tax attributes are utilized in a future period.

15. Product revenue, net

The following table presents the Company's net revenue by product (in thousands):

	Year Ended December 31,	
	2022	2021
Libmeldy	$ 18,796	$ —
Strimvelis	1,814	700
Total	$ 20,610	$ 700

Net product revenue of Libmeldy by geography consisted of the following and is attributable to individual countries based on the location of the customer as of December 31, 2022 (in thousands):

	Year ended December 31, 2022
United Kingdom	$ 6,322
Italy	5,544
France	3,883
Germany	3,047
Total Libmeldy revenue, net	$ 18,796

As of December 31, 2022 and 2021, all Strimvelis revenue was generated in Italy.

Activity in each of the product revenue allowance and reserve categories for Libmeldy is summarized as follows (in thousands):

	Trade Discounts and Allowances	Government rebates	Total
Balance as of December 31, 2021	$ —	$ —	$ —
Provision Related to sales in the current year	4,573	2,300	6,873
Credits and payments made during the period	(183)	—	(183)
Balance as of December 31, 2022	$ 4,390	$ 2,300	$ 6,690

The total reserves described above are summarized as components of the Company's consolidated balance sheets as follows (in thousands):

	December 31, 2022
Reduction of accounts receivable, net	$ 4,390
Component of accrued expenses and other current liabilities	2,300
Balance as of December 31, 2022	$ 6,690

There were no Libmeldy reserves or revenue allowances as of December 31, 2021. Strimvelis had no trade discounts and allowances or government rebates in the years ended December 31, 2022 and 2021.

16. Collaboration revenue

On July 1, 2021, the Company entered into a strategic collaboration with Pharming Group N.V. ("Pharming") to research, develop, manufacture, and commercialize OTL-105, an investigational *ex vivo* autologous HSC gene therapy for the treatment of hereditary angioedema (HAE), a life-threatening rare disorder that causes recurring swelling attacks in the face, throat, extremities and abdomen (the "Collaboration Agreement").

Under the terms of the Collaboration Agreement, Pharming was granted worldwide rights to OTL-105 and will be responsible for clinical development, regulatory filings and commercialization of the investigational gene therapy, including associated costs. The Company will lead the completion of IND-enabling activities and oversee manufacturing of OTL-105 during pre-clinical and clinical development, which will be funded by Pharming. In addition, both the Company and Pharming will explore the application of non-toxic conditioning regimen for use with OTL-105 administration.

The Company received an upfront payment of $10.0 million in cash from Pharming. The Company is also eligible to receive up to $189.5 million in development, regulatory and sales milestones as well as mid-single to low double-digit percentage royalty payments on future worldwide sales.

The Company also entered into a Share Purchase Agreement with Pharming on July 1, 2021 (the "SPA"), pursuant to which the Company issued 1,227,738 ordinary shares to Pharming for total consideration of $7.5 million. The consideration is payment for the fair value of ordinary shares with a fair value of $4.1 million plus a $3.4 million premium on the fair value of the Company's ordinary shares. The "Collaboration Agreement" and the "SPA" are referred to together as the "Pharming Agreements."

Accounting analysis

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 1,227,738 of the Company's ordinary shares as part of the SPA, and the license and collaboration agreement, which conveys the license and provides for the Company to provide research, development, manufacturing services for OTL-105. The Pharming Agreements were entered into concurrently as part of a single commercial objective and the Company considers them a single arrangement for accounting purposes. The total upfront payments of $17.5 million are comprised of $4.1 million attributed to the equity sold to Pharming and $13.4 million attributed to the Collaboration Agreement.

The Company has concluded that the conveyance of the license for the HAE program and the provision of research, development, and manufacturing services for the HAE program represent a series of distinct services that are accounted for as a single performance obligation within the Collaboration Agreement.

The Company determined that the transaction price includes: the $13.4 million attributed to the Collaboration Agreement and the variable consideration for estimated reimbursement payments at agreed upon contractual rates to be received from Pharming for the Company's on-going research, development, and manufacturing services. The potential future variable consideration is associated with the reimbursement for research, development, and manufacturing services provided by the Company to Pharming at agreed upon contractual rates which is the only remaining unsatisfied performance obligation. The milestone payments included in the Collaboration Agreement are fully constrained as a result of the uncertainty regarding whether any of the associated milestones will be achieved. The Company re-evaluates the transaction price as of the end of each reporting period.

The Company recognizes revenue associated with the performance obligation as the research, development, and manufacturing services are provided using an input method, based on the cumulative costs incurred compared to the total estimated costs expected to be incurred to satisfy the performance obligation. The transfer of control to the customer occurs over the time period that the research, development and manufacturing services are to be provided by the Company. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred consistent with the cost-to-cost method. The estimated costs associated with the remaining efforts required to complete the performance obligations may change which may materially impact revenue recognition and the Company regularly evaluates and, when necessary, updates the costs associated with the remaining efforts. Accordingly, revenue may fluctuate from period to period due to revisions to estimated costs resulting in a change in the measure of progress for the performance obligation or if the transaction price changes due to inclusion of any milestone payments that become unconstrained.

The following table summarizes research and development costs incurred and collaboration revenue recognized in connection with the Company's performance under the Collaboration Agreement (in thousands):

	Year Ended December 31,	
	2022	2021
Reimbursement revenue	$ 1,776	$ 843
Upfront and milestone payment revenue	269	132
Total	$ 2,045	$ 975

The Company had $0.5 million and $0.8 due from Pharming included in accounts receivable as of December 31, 2022 and 2021, respectively.

As of December 31, 2022, the Company had contract liabilities of $11.3 million, of which $1.0 million was classified as current and $10.3 million was classified as long-term in the consolidated balance sheets. The deferred revenue balance represents the portion of the upfront payments received related to the performance obligation that remains partially unsatisfied as of December 31, 2022.

17. Commitments and contingencies

Lease commitments

The Company leases office and laboratory space and has an embedded lease with AGC. Refer to Note 10 for further information on the terms of our lease agreements.

Manufacturing and technology development master agreement with AGC

On July 2, 2020, the Company entered into the AGC Agreement pursuant to which AGC will develop, manufacture, and supply certain viral vectors and conduct cell processing activities for certain Company development and commercial programs. Under the terms of the AGC Agreement, the Company is obligated to pay AGC for a minimum product manufacturing commitment, dedicated manufacturing and development resources, and for a lease component associated with the right of use of exclusive manufacturing suites within AGC's existing facilities. The following table outlines the annual commitments associated with the contract as of December 31, 2022 (in thousands):

Due in:	Product manufacturing commitments (1)	Dedicated manufacturing and development resources (2)	Exclusive transduction suites (3)	Total AGC Commitment
2023	$ 1,933	$ 5,655	$ 2,147	$ 9,735
2024	1,933	5,655	2,147	9,735
2025	966	2,827	1,074	4,867
Total manufacturing commitments	$ 4,832	$ 14,137	$ 5,368	$ 24,337

The tabular disclosure above has been translated from Euros to U.S. Dollars using an exchange rate of €1.00 to $1.07.

(1) The minimum product manufacturing commitments may be increased to the mid-seven figures per contract year upon achievement of certain milestones.

(2) The Company may increase or decrease the usage of dedicated development services on a rolling basis with between six and 12-months' prior written notice to AGC. The above table assumes continued usage of dedicated development services at current rates.

(3) Refer to Note 10 for further information on the embedded operating lease agreement

The Company incurred $13.7 million and $16.4 million in expenses related to the AGC Agreement in the years ended December 31, 2022 and 2021, respectively. The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The AGC Agreement may be extended for an additional two years by mutual agreement of the Company and AGC. The Company has the right to terminate the AGC Agreement at its discretion upon 12-month's prior written notice to AGC, and beginning no earlier than July 2, 2022, AGC has the right to terminate the AGC Agreement at its discretion upon 24-month's prior written notice to the Company. Each party may terminate the AGC Agreement upon prior notice to the other party for an uncured material breach that the breaching party does not cure within the notice period.

Other funding commitments

The Company has entered into several license agreements (see Note 13). In connection with these agreements the Company is required to make milestone payments and annual license maintenance payments or royalties on future sales of specified products.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

Indemnification agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners, and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and senior management that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2022 or 2021.

18. Benefit plans

The Company makes contributions to private defined contribution pension plans on behalf of its employees. The Company matches its employee contributions up to six percent of each employee's annual salary based on the jurisdiction in which the employees are located. The Company paid $1.6 million and $1.7 million, in matching contributions for the years ended December 31, 2022 and 2021, respectively.

19. Subsequent events

Ratio change

On February 10, 2023, the Company announced that the Company's Board of Directors approved a change to the ratio of the Company's ADSs to ordinary shares (the "ADS Ratio") from the previous ADS Ratio of one ADS to one ordinary share to a new ADS Ratio of one ADS to ten ordinary shares. The ratio change became effective on March 10, 2023. The change in the ADS Ratio had the same effect as a one-for-ten reverse ADS split and is intended to enable the Company to regain compliance with the Nasdaq minimum bid price requirement. As all financial statement and disclosure information is presented in ordinary share amounts, not ADSs, there was no impact to the consolidated financial statements and footnote disclosures.

Issuance of shares through 2023 Private Placement

On March 6, 2023, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") pursuant to which the Company agreed to sell, in an unregistered offering, up to an aggregate of (i) 99,166,900 shares, consisting of a combination of Ordinary Shares, nominal value £0.10 per share ("Ordinary Shares") and Non-Voting Ordinary Shares, nominal value £0.10 per share ("Non-Voting Ordinary Shares" and together with the Ordinary Shares, "Shares") and (ii) warrants to purchase an aggregate of 109,083,590 Ordinary Shares or Non-Voting Ordinary Shares (the "Warrants").

The 2023 Private Placement consists of two closings. The Company agreed to sell and issue in the initial closing of the 2023 Private Placement (i) 56,666,900 Shares and (ii) Warrants to purchase an aggregate of 62,333,590 Shares, at a purchase price of $6.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The initial closing of the 2023 Private Placement occurred on March 10, 2023. The Company received gross proceeds of approximately $34.0 million from the initial closing of the 2023 Private Placement, before deducting fees to the placement agent and other offering expenses payable by the Company.

In addition, the Company agreed to sell and issue in the second closing of the 2023 Private Placement (i) 42,500,000 Shares and (ii) Warrants to purchase an aggregate of 46,750,000 Shares, at a purchase price of $8.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The second closing is conditioned upon (x) the Company's announcement of its intention to file a biologics license application ("BLA") submission following receipt of the minutes from the U.S. Food and Drug Administration ("FDA") in connection with the Company's pre-BLA (Type B) meeting for OTL-200, provided such minutes do not expressly advise the Company not to proceed with a BLA submission, and (y) receipt of Shareholder Approval (as defined below) (collectively, the "Second Closing Trigger").

In connection with the Private Placement, the Company has agreed to hold a meeting of its shareholders no later than 120 days following the initial closing of the Private Placement to seek approval to give the Company's directors authority under s551 Companies Act 2006 to issue the securities to be issued and sold in the second closing of the Private Placement and the Shares issuable upon exercise of the Warrants to be issued and sold in the Private Placement, and to disapply pre-emption rights in respect of such authority under s570 of the Companies Act 2006 (collectively, "Shareholder Approval").

The second closing is expected to occur on the fifth trading day after the Company notifies the purchasing parties that the Second Closing Trigger has occurred and is subject to additional, customary closing conditions. If the Second Closing Trigger occurs, the Company anticipates receiving gross proceeds of approximately $34.0 million from the second closing of

the 2023 Private Placement, before deducting fees to the placement agent and other offering expenses payable by the Company.

Each Warrant will have an exercise price equal to $1.10 per Share in the event the Vesting Event (as defined below) occurs on or prior to December 31, 2024, and $0.95 per Share in the event the Vesting Event occurs after December 31, 2024. The Warrants will be exercisable during the 30 days following the Company's announcement of receipt of marketing approval of its BLA with respect to OTL-200 (the "Vesting Event"); provided that exercise of any Warrant is conditioned upon the receipt of Shareholder Approval. Commencement of the 30-day exercise period may be delayed as set forth in the Warrants in the event the Vesting Event occurs prior to Shareholder Approval. The Warrants will expire at the conclusion of the 30-day exercise period or, if the Vesting Event does not occur, March 10, 2026.

ORCHARD THERAPEUTICS PLC
CORPORATE AND OTHER INFORMATION

Board of Directors

Bobby Gaspar, M.D., Ph.D.
Director and Chief Executive Officer
Honorary Clinical Professor of Pediatrics and Immunology, the UCL Great Ormond Street Institute of Child Health

John T. Curnutte, M.D., Ph.D. (c) (d)
Director, Chair of the Science and Technology Committee
Senior Advisor, Samsara BioCapital

Alicia Secor (a) (b) (c)
Director
President, Chief Executive Officer of Atalanta Therapeutics, Inc.

Steven M. Altschuler, M.D. (d)
Director
Managing Director, Ziff Capital Partners

Marc Dunoyer (a) (c)
Director
Chief Executive Officer, Alexion, AstraZeneca Rare Disease

James Geraghty (c)
Director, Chairman of the Board of Directors, Chair of the Nominating and Corporate Governance Committee

Joanne T. Beck, Ph.D. (b) (d)
Director
Chief Technology Officer, Aerium Therapeutics

Charles A. Rowland, Jr. (a) (b)
Director, Chair of the Audit Committee, Chair of the Compensation Committee

Board Committees

(a) Audit Committee
(b) Compensation Committee
(c) Nominating and Corporate Governance Committee
(d) Science and Technology Committee

Executive Officers

Bobby Gaspar, M.D., Ph.D.
Director and Chief Executive Officer
Honorary Clinical Professor of Pediatrics and Immunology, the UCL Great Ormond Street Institute of Child Health

Frank Thomas
President and Chief Operating Officer

Registrar and Depositary

The registrar of our ordinary shares is Equiniti Limited, and the depositary is Citibank, N.A.

Stock Exchange Listing

Our American Depositary Shares, each representing ten ordinary shares, are listed on the Nasdaq Capital Market under the symbol "ORTX."

Annual Meeting

Our Annual General Meeting of Shareholders will take place at 9 am London time (4 am Eastern time) on Wednesday, June 14, 2023, at 245 Hammersmith Road, London W6 8PW.

Form 10-K Report

Our Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the Securities and Exchange Commission, is printed as part of this Annual Report. Additional copies are available without charge upon written request to:

Christopher York, Company Secretary
Orchard Therapeutics plc
245 Hammersmith Road London W6 8PW
United Kingdom
+44 (0) 203 808 8286