

Orchard Therapeutics plc

Annual Report and Financial Statements
for the Year Ended 31 December 2019

Registered Number: 11494381

UK FINANCIAL DOCUMENTS

INTRODUCTION AND CONTENTS

Orchard Therapeutics plc (the “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:

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The “Annual Report”, as mentioned throughout these UK financial documents, is comprised of the reports listed above and the Annual Report on Form 10-K (the “Form 10-K”) filed with the United States Securities and Exchange Commission (the “SEC”) on 27 February 2020. The Form 10-K is included in substantially their final form as filed with the SEC, except for Note 17 – Subsequent Events on page F-32, which has been added to the group financial statements subsequent to filing of Form 10-K for the purposes of this UK Annual Report. Additionally, the audit opinions from the Form 10-K have been removed as the group financial statements are covered by the independent auditors’ report over the group financial statements, included in this Annual Report on page 4. For the purposes of the UK Annual Report, the exhibits to the Form 10-K are not incorporated by reference.

COMPANY INFORMATION

| | |
|-----------------------------|--|
| Directors | James Geraghty, Chair of the Board of Directors Dr. Steven Altschuler (Appointed 3 February 2020) Joanne Beck Dr. John Curnutte (Appointed 30 August 2019) Marc Dunoyer Jon Ellis Bobby Gaspar Mark Rothera (Resigned 17 March 2020) Charles Rowland Alicia Secor Hong Fang Song (Resigned 26 June 2019) |
| Secretary | John Ilett |
| Registered Office | 108 Cannon Street London EC4N 6EU United Kingdom |
| Company Number | 11494381 |
| Independent Auditors | PricewaterhouseCoopers LLP 3 Forbury Place 23 Forbury Road Reading, Berkshire, RG1 3JH United Kingdom |

CERTAIN NOTE DISCLOSURES RELEVANT TO THE GROUP

Basis of Preparation

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

UK Statutory Disclosure Requirements

(i) Monthly average number of people employed

| Group | 2019 | 2018 |
|------------------------|------------|------------|
| UK | 86 | 42 |
| Offshore | 126 | 69 |
| Total employees | 212 | 111 |

The monthly average number of people employed by the company (including directors) in 2019 was 220 (2018: 120).

(ii) Employee costs (in thousands)

| Group | 2019 (\$ USD) | 2018 (\$ USD) |
|--|------------------|------------------|
| Salaries and bonuses | 41,939 | 23,771 |
| Share-based compensation expense | 19,425 | 6,766 |
| Benefits | 4,465 | 2,347 |
| Social insurance and social security costs | 3,657 | 2,381 |
| Total employee costs | 69,486 | 35,265 |

(iii) Auditor remuneration

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

| Group | 2019 (\$ USD) | 2018 (\$ USD) |
|---|------------------|------------------|
| Fees payable to the Company's auditors and its associates for the audit of the Company and consolidated financial statements for the year ended December 31, 2019 | 1,273 | 475 |
| Fees associated with our initial public offering (2018), follow-on offering (2019), and F-3 shelf registration statement (2019) | 210 | 2,495 |
| Fees associated with our corporate reorganization | – | 47 |
| Accounting research tool subscription | 3 | 3 |
| Total fees paid to PricewaterhouseCoopers LLP | 1,486 | 3,020 |

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. A resolution to reappoint PwC as the Group's auditors will be put to shareholders at the Company's 2020 Annual General Meeting ("AGM").

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

Report on the audit of the group financial statements

Opinion

In our opinion, Orchard Therapeutics plc's group financial statements (the "financial statements"):

- give a true and fair view of the state of the group's affairs as at 31 December 2019 and of its loss and cash flows for the year then ended;
- have been properly prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP"); and
- have been prepared in accordance with the requirements of the Companies Act 2006.

We have audited the financial statements, included within the Annual Report and Financial Statements (the "Annual Report"), which comprise: the Consolidated Balance Sheet as at 31 December 2019; the Consolidated Statement of Operations and Comprehensive Loss; the Consolidated Statement of Cash Flows, the Consolidated Statement of Convertible Preferred Shares and Shareholders' 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 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



- Overall group materiality: \$8.2 million (2018: \$4.75 million), based on 5% of loss before tax.
- Of the group's six reporting units, 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 the group level, gave us the evidence we needed.
- We relied on the work performed by PwC US, who performed full scope procedures over Orchard Therapeutics plc and Orchard Therapeutics (North America), along with certain procedures over Orchard Therapeutics (Europe) Limited. We also visited PwC US in February 2020 to ensure sufficient direction, supervision and review of their work.
- For our opinion on the group as a whole, the reporting units where we performed audit work accounted for 100% of group revenue and 98% of group loss before tax.
- Key Audit Matter - Orchard Therapeutics (Europe) Limited Research & Development Tax Credit Receivable
- Key Audit Matter - COVID-19

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

The scope of our audit

As part of designing our audit, we determined materiality and assessed the risks of material misstatement in the financial statements. In particular, we looked at where the directors made subjective judgements, for example in respect of significant accounting estimates that involved making assumptions and considering future events that are inherently uncertain. As in all of our audits we also addressed the risk of management override of internal controls, including evaluating whether there was evidence of bias by the directors that represented a risk of material misstatement due to fraud.

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.

Key audit matter

How our audit addressed the key audit matter

Orchard Therapeutics (Europe) Limited R&D Tax credit receivable

The Company carries out research and development activities and submits tax credit claims under one of two U.K. research and development tax relief programs: either the Small and Medium-sized Enterprises research and development tax relief ("SME") program or the Research and Development Expenditure Credit ("RDEC") program. Each year, management evaluates which tax credit program the Company is expected to be eligible for and records a reduction to research and development expense for the portion of the expense that it expects to qualify for credit under the program and ultimately be realised. This requires management to make judgments regarding whether the nature of the activities and expenditures will qualify for the tax credit and ultimately be realised based on the allowable reimbursable expense criteria established by the U.K. government. For the year ended 31 December 2019, the Company recorded £14.3 million as a reduction of research and development expense related to these programs and has a related tax credit receivable of £22.5 million as of 31 December 2019. There is therefore a risk that the Company may recognize an excessively high tax credit receivable due to overestimating the amount of eligible expenditure, and that consequently not all of the related tax credit receivable is recoverable.

We have performed the following procedures to address the key audit matter:

- Obtained management's detailed calculation, reconciled this to the trial balance and tested for mathematical accuracy;
- Tested a sample of expenses included in the claim, including staff costs, consumables, externally provided workers (EPWs) and subcontractor expenses to underlying supporting documentation;
- Tested the allocation of a sample of expenses to specific projects, given that this impacts which tax relief programme the expenses are eligible to be claimed under, and also impacts the EU State Aid cap calculation;
- Confirmed that the correct uplifts and tax rates are being applied in the calculation using HMRC sources; and
- Engaged with our R&D Tax specialists to assess the estimates included within the calculation and the basis on which the claim has been prepared, to ensure this is prepared in compliance with the relevant laws and regulations.

From the procedures performed, we identified an adjustment which was subsequently made by management.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

| Key audit matter | How our audit addressed the key audit matter |
|---|---|
| <p><i>COVID-19</i></p> <p>In December 2019, a novel strain of coronavirus (COVID-19) surfaced in China and has spread globally. The extent of the impact of the virus was not anticipated as at 31 December 2019 and it was not considered a global pandemic until after the year end, when this was declared by the World Health Organisation (WHO). Consequently, the impact of the virus is not considered an adjusting post balance sheet event for the purposes of these financial statements.</p> <p>As noted in the company's press release dated 31 March 2020, the coronavirus has had an impact on the global economy, and may impact the Group's ability, as well as the ability of the Group's customers and suppliers, to operate in a "business as usual" manner, which could have a material effect on the results of the business, financial condition or results of operations.</p> <p>Management have asserted in the press release that whilst the Group continues to progress its development, regulatory and commercialization plans, it also acknowledges impacts of COVID-19 on clinical activities, regulatory timelines and commercial readiness efforts that are underway, with the expectation that some of these will be delayed. The Group has considered the potential impacts noted above on its cash flow and liquidity position by performing various sensitivities and modelling scenarios to ensure that it has sufficient liquidity to continue as a going concern.</p> | <p>We have performed the following procedures to address the key audit matter:</p> <ul style="list-style-type: none">– Held discussions with management to understand, in qualitative terms, the impact of COVID-19 on business operations;– Evaluated management's sensitivities/modelling and challenged the key assumptions contained within the updated cash flow forecasts;– Assessed the reasonableness/achievability of management's mitigating actions; and– Read management's disclosures in the financial statements. <p>From the procedures performed, we found that management's analysis is supportable and that the disclosures within the financial statements are appropriate.</p> |

How we tailored the audit scope

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

The group is structured such that the significant majority of the business is comprised of two operating businesses, being Orchard Therapeutics (Europe) Limited and Orchard Therapeutics North America. The group financial statements are a consolidation of six reporting units, comprising the group's operating subsidiaries and centralised group functions. In establishing the overall approach to the group audit, we determined the type of work that needed to be performed at the reporting units.

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.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

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

| | |
|--|---|
| Overall group materiality | \$8.2 million (2018: \$4.75 million). |
| How we determined it | 5% of loss before tax. |
| Rationale for benchmark applied | Based on the benchmarks used in the Annual Report, loss before tax is the primary measure used by the shareholders in assessing the performance of the group, and is a generally accepted auditing benchmark. |

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 \$5.96 million to \$6.34 million.

We agreed with the Audit Committee that we would report to them misstatements identified during our audit above \$410,000 (2018: \$237,500) as well as misstatements below that amount that, in our view, warranted reporting for qualitative reasons.

Conclusions relating to going concern

We have nothing to report in respect of the following matters in relation to which ISAs (UK) require us to report to you where:

- the directors' use of the going concern basis of accounting in the preparation of the financial statements is not appropriate; or
- the directors have not disclosed in the financial statements any identified material uncertainties that may cast significant doubt about the group's ability to continue to adopt the going concern basis of accounting for a period of at least twelve months from the date when the financial statements are authorised for issue.

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

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 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 the responsibilities described above and our work undertaken in the course of the audit, ISAs (UK) require us also to report certain opinions and matters as described below.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

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 Strategic Report and UK Statutory Directors' Report for the year ended 31 December 2019 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 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 set out on pages 15 and 16, 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.

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 received 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.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

Other matter

We have reported separately on the parent company financial statements of Orchard Therapeutics plc for the period ended 31 December 2019.



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

• April 2020

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

Report on the audit of the parent company financial statements

Opinion

In our opinion, Orchard Therapeutics plc's parent company financial statements (the "financial statements"):

- give a true and fair view of the state of the parent company's affairs as at 31 December 2019;
- have been properly prepared in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 102 "The Financial Reporting Standard applicable in the UK and Republic of Ireland", and applicable law); and
- have been prepared in accordance with the requirements of the Companies Act 2006.

We have audited the financial statements, included within the Annual Report and Financial Statements (the "Annual Report"), which comprise: the Parent Company Balance Sheet as at 31 December 2019; 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 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



- Overall materiality: \$5.96 million (2018: \$1.3 million), based on 1% of total assets, reduced for an allocation of component materiality as part of the overall group audit.
- The audit comprised only the audit of Orchard Therapeutics plc
- Key Audit Matter – COVID-19

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. In particular, we looked at where the directors made subjective judgements, for example in respect of significant accounting estimates that involved making assumptions and considering future events that are inherently uncertain. As in all of our audits we also addressed the risk of management override of internal controls, including evaluating whether there was evidence of bias by the directors that represented a risk of material misstatement due to fraud.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

Key audit matters

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

Key audit matter

How our audit addressed the key audit matter

COVID-19

In December 2019, a novel strain of coronavirus (COVID-19) surfaced in China and has spread globally. The extent of the impact of the virus was not anticipated as at 31 December 2019 and it was not considered a global pandemic until after the year end, when this was declared by the World Health Organisation (WHO). Consequently, the impact of the virus is not considered an adjusting post balance sheet event for the purposes of these financial statements.

As noted in the company's press release dated 31 March 2020, the coronavirus has had an impact on the global economy, and may impact the company's ability, as well as the ability of the company's suppliers, to operate in a "business as usual" manner, which could have a material effect on the results of the business, financial condition or results of operations.

Management have asserted in the press release that whilst the company continues to progress its development, regulatory and commercialization plans, it also acknowledges impacts of COVID-19 on clinical activities, regulatory timelines and commercial readiness efforts that are underway, with the expectation that some of these will be delayed. The company has considered the potential impacts noted above on its cash flow and liquidity position by performing various sensitivities and modelling scenarios to ensure that it has sufficient liquidity to continue as a going concern.

We have performed the following procedures to address the key audit matter:

- Held discussions with management to understand, in qualitative terms, the impact of COVID-19 on business operations;
- Evaluated management's sensitivities/modelling and challenged the key assumptions contained within the updated cash flow forecasts;
- Assessed the reasonableness/achievability of management's mitigating actions;
- Read management's disclosures in the financial statements.
- From the procedures performed, we found that management's analysis is supportable and that the disclosures within the financial statements are appropriate.

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.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

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 materiality | \$5.96 million (2018: \$1.3 million). |
| How we determined it | 1% of total assets, reduced for an allocation of component materiality as part of the overall group audit. |
| 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 Company and reflects the Company's principal activity as a holding Company. We have adjusted this down to \$5.96 million on the basis of an appropriate component materiality for the group audit. |

We agreed with the Audit Committee that we would report to them misstatements identified during our audit above \$410,000 (2018: \$300,000) as well as misstatements below that amount that, in our view, warranted reporting for qualitative reasons.

Conclusions relating to going concern

We have nothing to report in respect of the following matters in relation to which ISAs (UK) require us to report to you where:

- the directors' use of the going concern basis of accounting in the preparation of the financial statements is not appropriate; or
- the directors have not disclosed in the financial statements any identified material uncertainties that may cast significant doubt about the parent company's ability to continue to adopt the going concern basis of accounting for a period of at least twelve months from the date when the financial statements are authorised for issue.

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

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.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

With respect to the 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 the responsibilities described above and our work undertaken in the course of the audit, the Companies Act 2006 and ISAs (UK) require us also to report certain opinions and matters as described below.

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 Strategic Report and UK Statutory Directors' Report for the year ended 31 December 2019 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 Strategic Report and UK Statutory Directors' Report.

Directors' Remuneration

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

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 set out on pages 15 and 16, 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.

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.

INDEPENDENT AUDITORS' REPORT TO THE MEMBERS OF ORCHARD THERAPEUTICS PLC

continued

Other required reporting

Companies Act 2006 exception reporting

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

- we have not received 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 2019.



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

- April 2020

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 accounting principles generally accepted in the United States of America (US GAAP) and parent company financial statements in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 102 "The Financial Reporting Standard applicable in the UK and Republic of Ireland", and applicable law). Under company law the 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 and parent company for that period. In preparing the financial statements, the directors are required to:

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

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

The directors are responsible for keeping adequate accounting records that are sufficient to show and explain the group 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

Each of the directors, whose names and functions are listed in UK Statutory Directors' Report confirm that, to the best of their knowledge:

- the parent company financial statements, which have been prepared in accordance with United Kingdom Generally Accepted Accounting Practice (United Kingdom Accounting Standards, comprising FRS 102 "The Financial Reporting Standard applicable in the UK and Republic of Ireland", and applicable law), give a true and fair view of the assets, liabilities, financial position and loss of the company;
- the group financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States of America, give a true and fair view of the assets, liabilities, financial position and loss of the group; and
- the UK Statutory Directors' Report includes a fair review of the development and performance of the business and the position of the group and parent company, together with a description of the principal risks and uncertainties that it faces.

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 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 and parent company's auditors are aware of that information.

UK STATUTORY STRATEGIC REPORT

The directors present their UK Statutory Strategic Report on the Group and the audited financial statements for the year ended 31 December 2019. The information in this document below that is referred to in the following table shall be deemed to comply with the UK Companies Act 2006 requirements for the UK Statutory Strategic Report:

| Required item in the UK Statutory Strategic Report | Company Response and where information can be found in the Annual Report on Form 10-K, if applicable |
|--|---|
| A fair review of the company's business, including use of key performance indicators | <p>Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations. Specifically, management addresses revenue, operating expenses, other income, direct research and development expenses by program, indirect research and development expenses, and selling, general, and administrative expenses. Additionally, management addresses liquidity and capital resources.</p> <p>The Company monitors the aforementioned key performance indicators on a monthly basis by analysing actual performance versus budget. We perform analysis of key cost drivers to monitor Company growth and cash flows.</p> |
| A description of the principal risks and uncertainties | Item 1A. Risk Factors. For discussion of the risks and uncertainties associated with COVID-19, refer to page 21 of the UK Statutory Directors' Report. |

| | |
|--------------------------------------|--|
| Information on environmental matters | The Company is required to measure and report its greenhouse gas emissions in accordance with the provisions of the Companies Act 2006 (UK Statutory Strategic Report and UK Statutory Directors' Report) Regulations 2013. Our greenhouse gas emissions estimates for 2019 has been prepared in accordance with the U.K. Government's Department for Environment, Food and Rural Affairs (Defra) guidance document "Environmental Reporting Guidelines: Including Mandatory GHG emissions reporting guidance, from March 2019". |
|--------------------------------------|--|

Year ended 31 December 2019
Tonnes carbon dioxide equivalent (tCO₂-e)

| | |
|--|-------|
| Estimated greenhouse gas emissions from purchased electricity, heat, steam, or cooling for our own use | 303.6 |
|--|-------|

| | |
|--|-----|
| Intensity ratio: Total greenhouse gas emissions per employee on the basis of a monthly average 212 full-time equivalent employees during the year ended 31 December 2019 | 1.4 |
|--|-----|

We have used evidence and estimates derived from evidence provided by our energy supply partners and lessors to generate our disclosure of emissions for the period. These include the purchase of electricity, heat, steam and cooling either directly from our energy supply partners, or through utility bills from our lessors. Standard emission factors from Defra's GHG Conversion Factory 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.

As we were only a listed company for two months in 2018, no GHG missions were measured or reported, and 2019 is our baseline year for GHG reporting.

UK STATUTORY STRATEGIC REPORT

continued

| Required item in the UK Statutory Strategic Report | Company Response and where information can be found in the Annual Report on Form 10-K, if applicable |
|---|--|
| Information about the company's employees | <p>Item 1. Business – Employees. Meetings are held with employees to discuss the operations and progress of the business. Senior Management and Board Members interact with employees of the Group and regularly visit the Group's facilities, thereby providing opportunities to engage in discussions with employees at various levels within the organization.</p> |
| Information about social, community and human rights issues | <p>The Group endeavors to impact positively on the community in which it operates through various charity donations and other charity events. The Group does not, at present, have a specific policy on human rights. However, we have several policies that promote the principles of human rights. We will respect the human rights of all our employees, including:</p> <ul style="list-style-type: none">• Provision of a safe, clean working environment• Ensuring employees are free from discrimination and coercion• Not using child or forced labor• Respecting the rights of privacy and protecting access and use of employee personal information <p>We also have an equal opportunities policy and a dignity at work policy, both of which promote the right of every employee to be treated with dignity and respect and not be harassed or bullied on any grounds.</p> <p>For information on compliance associated with anti-fraud and anti-bribery laws, refer to Item 1. Business – Government regulation – Other healthcare laws and compliance requirements.</p> |
| Description of the company's strategy | <p>Item 1. Business.</p> |
| Description of the company's business model | <p>Item 1. Business.</p> |

UK STATUTORY STRATEGIC REPORT

continued

| Required item in the UK Statutory Strategic Report | Company Response and where information can be found in the Annual Report on Form 10-K, if applicable | | | | | | | | | | | | | | | | | | | | | | |
|---|--|---------------|--------------|-----------------|-------------|---------------|--------------|---------------------|---|---|---|----------------------------|----|---|----|-----------------|----|-----|-----|-----------------|-----|-----|-----|
| Diversity | <p>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 2019 is as follows:</p> <table border="1"> <thead> <tr> <th>Position</th> <th>Male</th> <th>Female</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Company Directors**</td> <td>7</td> <td>2</td> <td>9</td> </tr> <tr> <td>Executives/Vice Presidents</td> <td>20</td> <td>9</td> <td>29</td> </tr> <tr> <td>Other Employees</td> <td>97</td> <td>127</td> <td>224</td> </tr> <tr> <td>Total Employees</td> <td>117</td> <td>136</td> <td>253</td> </tr> </tbody> </table> <p>**Includes our Chief Executive Officer and Chief Scientific Officer</p> | | | Position | Male | Female | Total | Company Directors** | 7 | 2 | 9 | Executives/Vice Presidents | 20 | 9 | 29 | Other Employees | 97 | 127 | 224 | Total Employees | 117 | 136 | 253 |
| Position | Male | Female | Total | | | | | | | | | | | | | | | | | | | | |
| Company Directors** | 7 | 2 | 9 | | | | | | | | | | | | | | | | | | | | |
| Executives/Vice Presidents | 20 | 9 | 29 | | | | | | | | | | | | | | | | | | | | |
| Other Employees | 97 | 127 | 224 | | | | | | | | | | | | | | | | | | | | |
| Total Employees | 117 | 136 | 253 | | | | | | | | | | | | | | | | | | | | |

Section 172(1) Companies Act 2006

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

| Section 172(1) Companies Act requirements | Company Response and where information can be found in the Annual Report on Form 10-K, or elsewhere in this Annual Report, if applicable. |
|---|--|
| the likely long-term consequences of any decision; | Item 1. Business. The Group will need substantial additional funding to support continuing operations and pursue a growth strategy as outlined in "Item 1. Business". 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 favorable terms, or at all. |
| the interests of the Company's employees; | Item 1. Business – Employees. The Board and Company management has 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 need to foster the Company's business relationships with suppliers, customers and others; | Item 1. Business – Manufacturing, and Item 1A. Risk Factors – Risks related to manufacturing and supply. |
| the impact of the Company's operations on the community and the environment; | The group has over 250 employees, operating at three locations in the San Francisco Bay Area, Boston, MA, and London, UK. Our greenhouse gas emissions associated with these facilities is disclosed on page 17 of this Annual Report. |

UK STATUTORY STRATEGIC REPORT

continued

| Section 172(1) Companies Act requirements | Company Response and where information can be found in the Annual Report on Form 10-K, or elsewhere in this Annual Report, if applicable. |
|--|--|
| the desirability of the Company maintaining a reputation for high standards of business conduct; | The Board of Directors of Orchard Therapeutics plc sets high standards for the Company's employees, officers and directors. Implicit in this philosophy is the importance of sound corporate governance. The Group operates Codes of Business Conduct and Ethics and provides mechanisms for whistle blowing and complaints, described in detail on the Group's website, under Corporate Governance. Employees are required to read and acknowledge these codes annually and to follow them at all times. |
| the need to act fairly as between shareholders of the Company | <p>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.</p> <p>Annual and interim results are communicated via press releases, and are filed with the U.S. Securities and Exchange Commission, as are operational and regulatory press releases. Shareholders may also attend the Annual General Meeting where they can discuss matters with the board.</p> |

On behalf of the Board of Directors

Bobby Gaspar
Director

[9] April 2020

UK STATUTORY DIRECTORS' REPORT

The directors of the Company submit this report and the audited financial statements as of and for the years ended 31 December 2019 and 2018. The information in this report, including the information that is referred to below in the following table, shall be deemed to comply with the UK Companies Act 2006 requirements for the UK Statutory Directors' Report:

| Required item in the UK Statutory Directors' Report | Company Response and where information can be found in the Annual Report on Form 10-K, if applicable. Some disclosures which would typically be included in the UK Statutory Strategic Report. |
|--|---|
| General Information | Item 1. Business. |
| Describe the principal activities of the group | Item 1. Business; Item 1A. Risk Factors. |
| Indication of the likely future developments of the group's business | Item 1. Business; Item 1A. Risk Factors. |
| Details of the recommended dividend | Not applicable – the directors do not recommend the payment of a dividend (2018: nil). |
| Indication of the group's research and development activities | Item 1. Business. |
| Level of political donations and political expenditure | None – the group has not made any political donations (2018: nil). |
| Particulars of any important post balance sheet events | <p><i>CEO Transition</i></p> <p>Effective as of 17 March 2020, Mark Rothera resigned his positions as President and Chief Executive Officer of Orchard Therapeutics plc (the "Company") and as a director of the Company.</p> <p>On 18 March 2020, the Company announced the appointment of Bobby Gaspar, M.D., Ph.D., as Chief Executive Officer of the Company, effective on March 18, 2020.</p> <p><i>Grants of Share Options to Employees and New Directors</i></p> <p>On 2 January 2020, the Company granted share options to employees and its former CSO (now CEO) for the purchase of an aggregate of 3,623,295 ordinary shares at an exercise price of \$13.58 per share, split 3,423,295 to employees and 200,000 to the former CSO (now CEO).</p> <p>On 3 February 2020, the Company granted share options to employees and one new Director for the purchase of an aggregate of 336,567 ordinary shares at an exercise price of \$12.30 per share. Included in this amount is a grant of 50,000 share options to our new Director, Dr. Steven Altschuler, who was appointed to the Board of Directors on 3 February 2020.</p> <p>On 2 March 2020, the Company granted share options to employees and one new Director for the purchase of an aggregate of 126,250 ordinary shares at an exercise price of \$12.05 per share.</p> <p>On 1 April 2020 the Company granted share options to our CEO and President and Chief Operating Officer for the purchase of an aggregate of 450,000 ordinary shares at an exercise price of \$7.05 per share.</p> <p>On 1 April 2020, The Company also granted performance-based RSUs to its CEO covering a maximum of 195,000 ordinary shares. These performance-based RSUs will vest, if at all, based upon attainment of certain clinical and regulatory milestones, but must vest by 2 December 2024 or else be forfeited.</p> |

UK STATUTORY DIRECTORS' REPORT

continued

| Required item in the UK Statutory Directors' Report | Company Response and where information can be found in the Annual Report on Form 10-K, if applicable |
|--|--|
| Particulars of any post balance sheet events: COVID-19 Risks and Uncertainties | <p>COVID-19 Risks and Uncertainties</p> <p>Since 31 December 2019, a novel strain of coronavirus, now referred to as COVID-19 has continued to spread globally, has been declared a pandemic by the World Health Organization and has spread to over 100 countries, including the United States and United Kingdom. The impact of this pandemic has been and will likely continue to be extensive in many aspects of society, which has resulted in and will likely continue to result in significant disruptions to the global economy, as well as businesses and capital markets around the world.</p> <p>The Group and the Company is subject to risks associated with the COVID-19 pandemic. In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy, have placed significant restrictions on travel. Limitations on travel and other social distancing measures may have an effect on our clinical activities and regulatory timelines. Travel and stay-at-home orders could adversely affect our contract manufacturers and third-party logistics providers. Shelter-in-place and stay-at-home orders in California has caused the Group and the Company to temporarily suspend construction activities on our planned manufacturing facility in Fremont, California. Commercial activity associated with our EMA-approved gene therapy for ADA-SCID, Strimvelis, has been postponed by the treatment site and scheduled patients are continuing to receive enzyme replacement therapy until treatment with Strimvelis can occur. Any prolonged material disruptions to the Group and the Company's employees, suppliers, contract manufacturers, vendors, or patients could impact our operating results and could lead to impairments. The Group and the Company's ability to access the capital markets could be impacted if disruptions in the capital markets continue. The value of the investment in subsidiaries held by the Company could also be impaired if the recoverable amount of the companies in which an investment is held falls below the carrying value of the total investment.</p> |
| Names of all directors and their interests | Refer to the Directors' Shareholding table included in the Director's Remuneration Report, on page 50 of this annual report, and the Company Information on page 2 of this annual report. |
| Statement on directors' third-party indemnity provision | 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 remains in force as at the date of approving the UK Statutory Directors' Report. |
| The financial risk management objectives and policies of the entity, including the policy for hedging each major type of forecasted transaction for which hedge accounting is used | Not applicable – the Company does not engage in hedging activities (2018: none). |

Group Annual Report and Financial Statements

for the year ended 31 March 2018

| Required item in the UK Statutory Directors' Report | Company Response and where information can be found in the Annual Report on Form 10-K, if applicable |
|--|--|
| The exposure of the entity to: Credit risk | Item 15(a)(1). Financial Statements. Refer to Note 2. Summary of Significant Accounting Policies – Concentration of credit risk. |
| Liquidity risk | Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations. |
| Exchange rate and cash flow risk | Item 1A. Risk Factors – "Exchange rate fluctuations may materially affect our results of operations and financial condition". Item 7A. Quantitative and Qualitative Disclosures About Market Risk – Foreign currency exchange risk. |
| Disclosures on purchases of own shares during the year | Not applicable – the Group has not purchased or placed a charge on its own shares in the year (2018: none). |
| Branches outside the UK | Item 15(a)(3). Exhibit 21.1 – List of Subsidiaries |
| Going Concern | At 31 December 2019, the Group held cash and cash equivalents and marketable securities of \$325.0 million and the Company held cash and marketable securities of \$244.0 million. The directors have prepared a forecast through 2021 which shows sufficient cash to fund planned research and development, commercial, and operating costs of the Group and the Company. The directors have considered the effect of the COVID-19 pandemic on our forecast, and have determined it does not have an effect on our ability to operate as a going concern for at least 12 months from the issuance of these consolidated financial statements. Therefore, the directors have at the time of approving the financial statements, a reasonable expectation that the Group and Company has adequate resources to continue in operational existence for the foreseeable future. Accordingly, the Company continues to adopt the going concern basis of accounting in preparing the financial statements. |
| Information on contracts of significance | Except as otherwise disclosed in the Form 10-K (including the exhibits thereto), the Company is not currently, and has not been in the last two years, party to any material contract, other than contracts entered into in the ordinary course of business. |
| Information on corporate governance practices | Item 10. The information required under item 10 is incorporated by reference to our definitive proxy statement for our 2020 annual general meeting to be filed with the U.S. Securities and Exchange Commission. |
| Independent Auditors | PricewaterhouseCoopers LLP have expressed their willingness to continue in office as auditors for another year. In accordance with Section 489 of the 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. |
| Annual General Meeting | The Annual General Meeting will be held in London on 17 June 2020. Further details will be provided to shareholders in due course. |

On behalf of the Board of Directors

Bobby Gaspar
Director

[9] April 2020

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 2019 (the "Remuneration Report").

The Company's Annual Report and Financial Statements, along with the Remuneration Report, will be subject to an advisory vote at the forthcoming Annual General Meeting on 17 June 2020 (the "AGM").

Introduction

Our executive compensation program seeks to incentivize and reward strong corporate performance. Highlights of our 2019 corporate performance are set forth below.

Clinical and Regulatory

MLD European MAA submission: The Marketing Authorization Application ("MAA") for OTL-200 for the treatment of metachromatic leukodystrophy ("MLD") was filed and accepted for review by the European Medicines Agency ("EMA") in November 2019, ahead of previous guidance.

Cryopreserved gene therapy formulations: Similar engraftment profiles were observed between the cryopreserved and fresh formulations of OTL-200 for MLD and OTL-101 for the treatment of adenosine deaminase severe combined immunodeficiency ("ADA-SCID"), which represents an important achievement toward the potential approvals of these investigational gene therapies and a key step toward global patient availability.

WAS registrational data set: The registrational trial for OTL-103 for the treatment of Wiskott-Aldrich syndrome ("WAS") met its key primary and secondary endpoints (n=8 at three years), including the elimination of severe bleeding episodes and a significant reduction in the frequency of severe infections.

MPS-I global license: The Company signed an exclusive license with Fondazione Telethon and Ospedale San Raffaele in Milan, Italy, for a clinical-stage HSC gene therapy program—OTL-203, a treatment for mucopolysaccharidosis type I ("MPS-I") that has shown promising early data in an ongoing proof-of-concept clinical trial.

Corporate Financings

Credit facility: In May 2019, we secured a five-year senior credit facility for up to \$75 million with MidCap Financial (Ireland) Limited ("MidCap Financial").

Follow-on public offering: In June 2019, we completed a follow-on public offering for net proceeds of approximately \$130 million, after deducting underwriting discounts and commission and offering expenses paid by us.

The global marketplace for talent

Orchard is a global biopharmaceutical company with major operations in the United States and Europe. The Company intends for both regions to be areas of high growth and great importance

DIRECTORS' REMUNERATION REPORT

continued

both now and in the future. Given that the market for experienced directors and biopharmaceutical executive talent is very competitive, particularly in the United States, the Committee references the US market as the leading indicator for remuneration levels and practices. This will help 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.

It can be difficult for Orchard, as a global company with operations in multiple major global regions to have remuneration arrangements that satisfy all local jurisdiction requirements and market demands. In taking any actions, the Committee is mindful of the general UK compensation framework, including investor bodies' guidance, and has considered these when determining the remuneration programs and policies where it believes they best serve the long-term interests of shareholders.

Pay for Performance

We believe that a significant portion of remuneration of our Executive Directors should be based on achieving objectives designed to create inherent value in the Company, and ultimately on achieving value creation for our shareholders. In line with this belief, the compensation of our Executive Directors includes both short and long-term incentives based on strategic goals. Similarly, our Non-Executive Directors receive equity incentives designed to reward long-term value creation for our shareholders.

2019 remuneration outcome

The Compensation Committee approved increases in base salary effective as of 1 January 2020. The salary for the Chief Executive Officer ("CEO") was increased by 3% to \$543,300. The Chief Scientific Officer ("CSO") was promoted in 2019 to the title of President of Research and CSO, and his salary was increased by 29% to £338,500 for his new role, and his target bonus was increased from 35% to 40% of salary for 2020. The target bonus for the CEO remains at 50% of salary.

As outlined above, a core principle in Orchard's remuneration program is the linkage between pay and performance. In financial year 2019, the annual bonuses paid to our Executive Directors, Mark Rothera, our CEO, and Bobby Gaspar, our CSO, were based on achieving the 2019 Company objectives, and in the case of our CSO, was also based on his individual performance. In light of the exceptional performance of the Executive Directors in 2019 in terms of their strong cross-functional leadership and the role this played in delivering exceptional overall Company performance, the Committee reviewed the 2019 corporate goals and based on the results approved a total outcome of 140% and 145% of target respectively for the CEO and CSO, resulting in a total bonus payout of 70% of the CEO's base salary and 51% of the CSO's base salary for the financial year ended 31 December 2019. The bonuses were paid in February 2020 and March 2020 for the CSO and CEO respectively. Please see page 46 of the Remuneration Report for additional information on the pay for performance linkage for these bonus outcomes.

Option awards were made under the 2018 Share Option and Incentive Plan to the two Executive Directors in 2019. The CEO was granted 415,000 options, and the CSO was granted 50,000 options, in each case at \$12.54 per share. The CSO was further granted 18,750 performance-based restricted shares ("PSUs").

DIRECTORS' REMUNERATION REPORT

continued

Changes to the Board and Chief Executive Officer

Dr. Steven Altschuler was appointed as a Non-Executive Director of the Company, effective as of 3 February 2020, and will be serving the Board's Science and Technology Committee. Further information is set out in the statement of implementation for 2020 on page 52.

On 18 March 2020, Bobby Gaspar was promoted to Chief Executive Officer. In connection with his promotion, Dr. Gaspar's annual base salary was increased to £440,000, his target annual bonus opportunity was increased to 60% of his base salary, and he was granted an option to purchase 300,000 of the Company's ordinary shares, effective 1 April 2020. The foregoing options will vest in equal monthly installments over four years commencing on the date of grant. In addition, Dr. Gaspar received a one-time grant of 195,000 PSUs, effective 1 April 2020. This PSU 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 Company through 2 January 2024. The milestones relate to achievement of specific clinical and regulatory milestones. While this information is included in the current report for full disclosure, the 2019 Directors' Remuneration Report refers to Mark Rothera as CEO, as he was the Chief Executive Officer throughout the 2019 financial year. Mr. Rothera stepped down from his position as President and Chief Executive Officer and resigned as a director of the Company on 17 March 2020.

Conclusion

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

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

Yours sincerely,

Charles Rowland, Jr.

Chair of the Compensation Committee

[9] April 2020

DIRECTORS' REMUNERATION REPORT

continued

Remuneration Policy

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

Key considerations when determining the Remuneration Policy

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

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

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

DIRECTORS' REMUNERATION REPORT

continued

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 | | | |
| <p>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.</p> <p>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.</p> | <p>Salaries are normally reviewed annually, and changes are generally effective from 1 January each year.</p> <p>The annual salary review for Executive Directors takes a number of factors into consideration, including:</p> <ul style="list-style-type: none"> • 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. | <p>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.</p> <p>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.</p> <p>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.</p> | <p>Executive Directors' performance is a factor considered when determining any salary increases.</p> |

DIRECTORS' REMUNERATION REPORT

continued

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. | <p>The Company aims to offer benefits that are in line with market practice.</p> <p>The main benefits currently provided include private health insurance, long-term disability, critical illness and death in service.</p> <p>Under certain circumstances the Company may offer relocation allowances or assistance. Expatriate benefits may be offered where required.</p> <p>Travel and any reasonable business-related expenses (including tax thereon) may be reimbursed.</p> <p>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.</p> | The value of each benefit is not predetermined and is typically based upon the cost to the Company of providing said benefit. | Not performance related. |
| Pensions | | | |
| The Company aims to provide a contribution towards life in retirement. | Executive Directors are eligible to receive employer contributions to the Company's Group Personal Pension Scheme or to a 401k plan or a salary supplement in lieu of pension benefits, or a mixture of both. | Up to 6% of salary per annum for Executive Directors. | Not performance related. |

DIRECTORS' REMUNERATION REPORT

continued

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. | <p>The maximum target bonus opportunity for Executive Directors is 80% of salary, with a maximum bonus opportunity of up to two times the target opportunity.</p> <p>For threshold performance, no more than 50% of target bonus may be payable.</p> <p>For 2020, the target bonus opportunity for Executive Directors will be no more than 50% of salary, with a maximum bonus opportunity of up to 150% of the target opportunity.</p> | <p>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.</p> <p>The annual bonus will be based on strategic goals, which may include financial, strategic and personal objectives.</p> <p>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 period.</p> |

DIRECTORS' REMUNERATION REPORT

continued

Executive Directors

| Purpose and link to strategy | Operation | Maximum opportunity | Performance metrics |
|---|---|--|---|
| 2018 Share Option and Incentive Plan ("SOIP") | | | |
| <p>The SOIP is designed to incentivise the successful execution of business strategy over the longer term and provide long-term retention.</p> <p>Facilitates share ownership to provide further alignment with shareholders.</p> | <p>The Committee will select the most appropriate form of SOIP award(s) each year.</p> <p>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.</p> <p>Currently, options normally vest over a period of four years on a monthly basis. Initial grants generally vest 25% after one year, and monthly thereafter for 36 months. 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.</p> <p>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.</p> | <p>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.</p> | <p>Performance conditions may apply to awards. Such conditions may be strategic objectives which may include milestones events, financial, strategic and/or personal objectives.</p> <p>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.</p> <p>Any performance conditions set will be designed to incentivise performance in support of the Company's strategy and business objectives.</p> <p>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.</p> <p>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 period.</p> |

DIRECTORS' REMUNERATION REPORT

continued

Executive Directors

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

DIRECTORS' REMUNERATION REPORT

continued

Chair and 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. | <p>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.</p> <p>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.</p> <p>When reviewing fee levels, account is taken of market movements in fee levels, Board committee responsibilities, ongoing time commitments and the general economic environment.</p> <p>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.</p> <p>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.</p> | <p>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.</p> <p>Actual fee levels are disclosed in the annual Directors' Remuneration Report for the relevant financial year.</p> | Not performance related. |

DIRECTORS' REMUNERATION REPORT

continued

Chair and Non-Executive Directors

| Purpose and link to strategy | Operation | Maximum opportunity | Performance metrics |
|--|--|---|--------------------------|
| Equity Awards | | | |
| To facilitate share ownership and provide alignment with shareholders. | <p>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.</p> <p>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.</p> <p>Currently any initial equity awards normally vest one- third after one year, and monthly thereafter for 24 months, and any annual awards normally vest monthly over three years.</p> | <p>There is no maximum award level for equity awards to Non-Executive Directors.</p> <p>The size of the equity awards is determined by the full Board of Directors, upon recommendation of the Compensation Committee.</p> <p>When reviewing award levels, account is taken of market movements in equity awards, Board committee responsibilities, ongoing time commitments and the general economic conditions.</p> | Not performance related. |

Notes to the policy table

Legacy arrangements

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

Performance conditions

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

DIRECTORS' REMUNERATION REPORT

continued

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

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

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

Differences in remuneration policy between Executive Directors and other employees

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

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

Committee discretion in operation of variable pay schemes

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

DIRECTORS' REMUNERATION REPORT

continued

These include the following:

- selecting the participants in the plans on an annual basis;
- determining the timing of grants of awards and/or payments;
- determining the quantum of awards and/or payments (within the limits set out in the policy table above);
- determining the choice (and adjustment) of performance measures and targets for each incentive plan in accordance with the policy set out above and the rules of each plan;
- determining the extent of vesting based on the assessment of performance and discretion relating to measurement of performance in certain events such as a change of control or reconstruction;
- making the appropriate adjustments required in certain circumstances, for instance for changes in capital structure;
- determining “good leaver” status, if applicable, for incentive plan purposes and applying the appropriate treatment; and
- undertaking the annual review of weighting of performance measures and setting targets for the annual bonus plan and other incentive schemes, where applicable, from year to year.

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

Shareholder views

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

Employment conditions

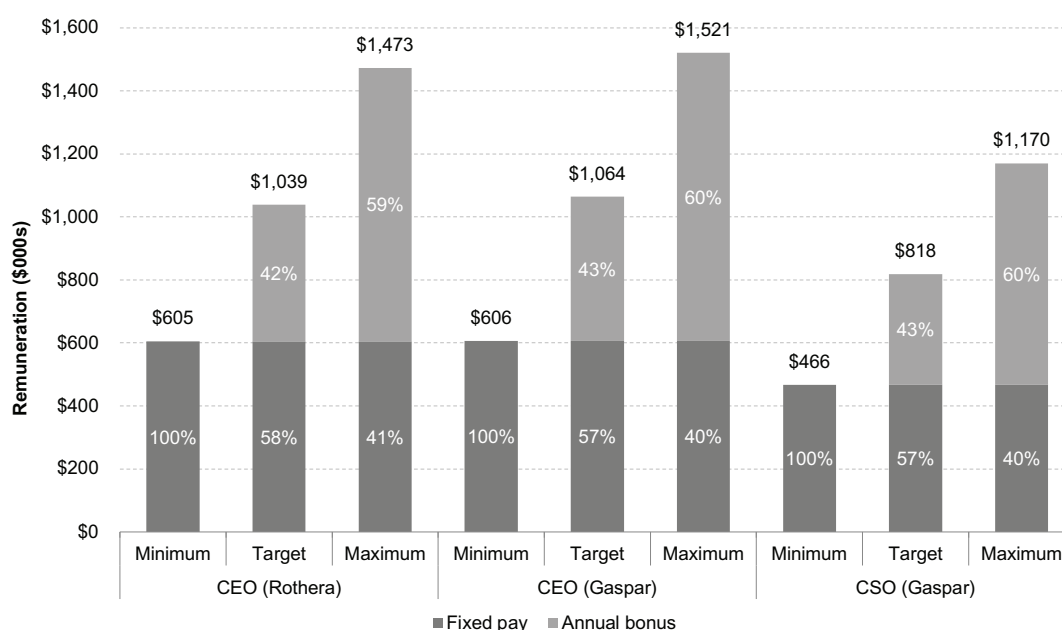
The Committee is regularly updated throughout the year on pay and conditions applying to Company employees. Where significant changes are proposed to employment conditions elsewhere in the Company these are highlighted for the attention of the Committee at an early stage.

DIRECTORS' REMUNERATION REPORT

continued

Remuneration scenarios for Executive Directors

The charts below show an estimate of the 2020 remuneration package for the Executive Directors under three assumed performance scenarios and these scenarios are based upon the remuneration policy set out above. The chart includes information related to our former CEO, Mark Rothera, which would have been his potential compensation prior to his resignation on 17 March, 2020. The chart also includes information related to our current CEO, Bobby Gaspar, in both his role as CEO, and his former role as CSO.



Notes to the scenario charts:

1. Minimum scenario comprises of fixed pay only, which includes the 2020 annual base salaries of \$543,300, \$572,000 and \$440,000 for the CEO Rothera), CEO (Gaspar) and CSO, respectively, benefits values as provided in the single total figure remuneration table, and pension contribution of up to 6% of salary. Mr. Gaspar's salary utilized in the chart above of £440,000 as CEO and £338,500 as CSO have been translated to USD at a rate of \$1.30 to £1.00 for comparability.
2. Target scenario comprises of fixed pay as set out above, and bonus pay-outs assuming on-target performance, as set in the policy, at a maximum target of 80% of salary for the executive directors.
3. Maximum scenario comprises of fixed pay as set out above, and 100% of maximum bonus pay-out, which is set in the policy at two times of the maximum target of 80% of salary for the executive directors.

The variable remuneration in the charts above only include annual bonus opportunity. The Executive Directors will additionally receive awards under the SOIP in 2020, in the form of market value options and PSUs. The maximum and target value of any equity awards under the plan is not defined, and, therefore, the awards cannot be valued nor included in the charts. Consequently, no share price growth has been factored into the chart.

DIRECTORS' REMUNERATION REPORT

continued

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.

DIRECTORS' REMUNERATION REPORT

continued

Other cash or equity-based awards

Executive Directors may receive awards under the SOIP on appointment. The Committee will assess and determine the award level, award vehicle, performance conditions and vesting schedule for each individual on a case-by-case basis. In addition, Executive Directors are eligible to participate in the ESPP subject to the conditions set forth therein.

In addition, the Committee may offer additional cash and/or equity-based elements in order to "buy-out" remuneration relinquished on leaving a former employer. Any awards made in this regard may have no performance conditions, or different performance conditions, or a different vesting schedule compared to the Company's existing plans, as the Committee considers appropriate. Depending on the timing and responsibilities of the appointment, it may be necessary to set different annual bonus or SOIP performance measures and targets as applicable to other Executive Directors.

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

Service contracts and termination policy

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

| Name | Position | Date of service contract | Notice period |
|---------------------|--------------------------|---------------------------------|-----------------------|
| Mark Rothera | Chief Executive Officer | 30 May 2019 | 60 days either party |
| Bobby Gaspar | Chief Scientific Officer | 2 January 2018 | 6 months either party |

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

DIRECTORS' REMUNERATION REPORT

continued

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 awards 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. |

DIRECTORS' REMUNERATION REPORT

continued

| | 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. | <p>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.</p> <p>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).</p> |

DIRECTORS' REMUNERATION REPORT

continued

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).

On 17 March, 2020, the Company entered into a Separation Agreement and Release with Mr. Rothera (the "Rothera Separation Agreement"), which provides, among other things, that Mr. Rothera will receive (i) an amount equal to 12 months of his base salary, payable in substantially equal installments in accordance with the Company's payroll practice over 12 months, provided that Mr. Rothera has not breached any of his continuing obligations, (ii) a pro-rated bonus representing Mr. Rothera's 50% target bonus for 2020, and (iii) reimbursement of COBRA premiums for health benefit coverage for up to 12 months, in an amount equal to the monthly employer contribution that the Company would have made to provide health insurance to Mr. Rothera had he remained employed with the Company. Additionally, all time-based equity awards held by Mr. Rothera that would have vested had Mr. Rothera remained employed by the Company for an additional 12 months following March 17, 2020 shall immediately vest and become fully exercisable or non-forfeitable. With respect to vested awards held by Mr. Rothera as of the date of his separation, the Company has agreed to extend the exercise period until the earlier of (a) the original expiration date for such vested awards or (b) 12 months after the date of his separation. After taking into account the acceleration of time-based equity awards described above, the unvested equity awards held by Mr. Rothera at the time of his separation will not be exercisable, unless a change in control of the Company occurs within three months of Mr. Rothera's separation, in which case such unvested equity awards will be accelerated in full. If a change in control does not occur within three months following Mr. Rothera's separation, such unvested portion of his equity awards shall terminate or be forfeited on the three month anniversary of Mr. Rothera's separation.

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. Neither Executive Director currently holds 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.

DIRECTORS' REMUNERATION REPORT

continued

The dates of appointment of each of the Non-Executive Directors serving at 31 December 2019 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). Dates after year end are for newly appointed Non-Executive Directors.

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

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

Annual Report on Remuneration

This part of the report has been prepared in accordance with Part 3 of The Large and Medium-sized Companies and Groups (Accounts and Reports) (Amendment) Regulations 2013 as amended and Rule 9.8.6 of the Listing Rules. Since the Company is not FTSE-listed, it is under no obligation to comply with the UK Corporate Governance Code, but best practice and good governance have been considered when preparing this report. The Annual Report on Remuneration and the Annual Statement by the Chair of the Compensation Committee will be put to a single advisory shareholder vote at the AGM on 17 June 2020.

Compensation Committee (the "Committee")

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

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

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

Meetings attendance (since 1 January 2019)

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

DIRECTORS' REMUNERATION REPORT

continued

Independent advisors

Wholly independent advice on executive remuneration is received from the Executive Compensation practice of Aon plc. Aon is a member of the Remuneration Consultants Group and is a signatory to its Code of Conduct. Aon advises on remuneration arrangements and all aspects of senior executive remuneration. In 2019, Aon assisted with the Committee and kept the Committee up to date on remuneration trends. During the 2019 financial year, fees charged by Aon for advice provided to the Committee for 2019 amounted to \$175,000 (excluding VAT). In addition, Aon provided advice to the Company's Human Resources function on implementation, which the Committee considers in no way prejudices Aon's position as the Committee's independent advisor. Goodwin Procter LLP have also advised the Company's Human Resources function on compensation.

Activity in the period

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

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

- evaluating the efficacy of the Company's remuneration policy and strategy;
- reviewing and determining remuneration to be paid to the Company's executive officers and directors, including setting the executive remuneration policy;
- reviewing and making recommendations to the Board regarding remuneration for non-executive members of the Board, including the approval of the director remuneration policy;
- agreeing the design of all share incentive plans;
- prepare any report on executive remuneration required by the rules and regulations of the US Securities and Exchange Commission, The Nasdaq Stock Market LLC and as required under UK law;
- reviewing, evaluating, and approving employment agreements, severance agreements, change-of-control protections, corporate performance goals and objectives, and other compensatory arrangements of the executive officers and other senior management and adjusting remuneration, as appropriate;
- evaluating and approving remuneration plans and programs and establishing equity remuneration policies;
- reviewing remuneration practices and trends to assess the adequacy and competitiveness of the executive remuneration programs as compared to industry peers, and determining the appropriate levels and types of remuneration to be paid;
- approving any loans by the Company to employees;
- reviewing and approving remuneration arrangements for any executive officer involving any subsidiary, special purpose or similar entity, with consideration of the potential for conflicts of interest; and
- reviewing the Company's practices and policies of employee remuneration as they relate to risk management and risk-taking incentives.

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

DIRECTORS' REMUNERATION REPORT

continued

Statement of shareholder voting at 2019 AGM

At last year's AGM held on 26 June 2019, 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 | 98.2% | 36,304,691 | 1.8% | 669,446 | 0% | 750 |
| To approve the Directors' Remuneration Policy | 91.6% | 33,863,941 | 8.4% | 3,110,196 | 0% | 750 |

Single total figure of Directors' remuneration – year ended 31 December 2019 (audited)

The total remuneration of the individual Directors who served in the year ended 31 December 2019, is shown below. Total remuneration is the sum of emoluments plus Company pension contributions. Total remuneration of the Individual Directors in the year ended 31 December 2018 is for the 2 months after the Company's listing on the Nasdaq from 31 October 2018 to 31 December 2018. The below table has been presented in US dollars (\$) which is the functional currency of the reporting entity:

| | | Base salary | Benefits ¹ | Pension | Bonus ² | SOIP ³ | Other ⁴ | Total remuneration |
|--------------------------------|-------------|--------------|-----------------------|-----------|--------------------|-------------------|--------------------|--------------------|
| | | /fees | | | | | | |
| Executive Directors | | | | | | | | |
| Mark Rothera | 2019 | 527 | 32 | 11 | 369 | 2,888 | 77 | 3,904 |
| | 2018 | 100 | 7 | 4 | 50 | 350 | 44 | 555 |
| Bobby Gaspar | 2019 | 344 | – | – | 174 | 503 | – | 1,021 |
| | 2018 | 55 | – | – | 33 | 68 | – | 156 |
| Non-Executive Directors | | | | | | | | |
| Joanne Beck | 2019 | 41 | – | – | – | 266 | – | 307 |
| | 2018 | 7 | – | – | – | 20 | – | 27 |
| Marc Dunoyer | 2019 | 47 | – | – | – | 322 | – | 369 |
| | 2018 | 8 | – | – | – | 29 | – | 37 |
| Jon Ellis | 2019 | – | – | – | – | – | – | – |
| | 2018 | – | – | – | – | – | – | – |
| Hong Fang Song | 2019 | – | – | – | – | – | – | – |
| | 2018 | – | – | – | – | – | – | – |
| James Geraghty | 2019 | 83 | – | – | – | 631 | – | 714 |
| | 2018 | 14 | – | – | – | 81 | – | 95 |
| Charles Rowland | 2019 | 60 | – | – | – | 269 | – | 329 |
| | 2018 | 10 | – | – | – | 20 | – | 30 |
| Alicia Secor | 2019 | 43 | – | – | – | 292 | – | 335 |
| | 2018 | – | – | – | – | 24 | – | 24 |
| John Curnutte | 2019 | 16 | – | – | – | 50 | – | 66 |
| | 2018 | – | – | – | – | – | – | – |
| Total | 2019 | 1,161 | 32 | 11 | 543 | 5,221 | 77 | 7,045 |
| | 2018 | 194 | 7 | 4 | 83 | 592 | 44 | 924 |

1. For Executive Directors, included private health insurance, long term disability, critical illness and death in service benefits.
2. Bonus for our Executive Directors for 2018 was calculated on an accrual basis for the 2 months after the Company's listing on the Nasdaq. Bonus for our Executive Directors for 2019 was paid in February 2020.
3. SOIP options do not have performance conditions and have therefore been included based on the proportion of expense incurred on a straight-line basis during the period based on their Black Scholes estimated value at date of grant. 2018 comparators have been restated using the same approach, resulting in restated total remuneration for 2018.
4. Other expenses include payments for relocation/housing benefits and tax-related services.

DIRECTORS' REMUNERATION REPORT

continued

2019 Annual bonus (audited)

In 2019, the CEO and CSO's annual bonus outcome of 140% and 145% of target, respectively resulted in a total bonus pay out of 70% of the CEO's base salary and 51% of the CSO's base salary for the financial year ended 31 December 2019.

During a series of meetings in December 2019 and January 2020, the Compensation Committee evaluated achievement of the 2019 corporate objectives and each Executive Director's individual performance. The Compensation Committee reviewed the following corporate goals and based on the results approved a 140% achievement level of the 2019 corporate objectives as the Company exceeded the target goals. The goals were as follows:

Corporate Goals and Achievements

- **Advance lead three clinical programs to regulatory filing: enable a filing with the U.S. Food and Drug Administration ("FDA") in 2020 for OTL-101 for the treatment of ADA-SCID, enable a filing with the EMA in 2020 for OTL-200 for the treatment of MLD, and enable filings with each of the EMA and FDA in 2021 for OTL-103 for the treatment of WAS** – Our key achievements in 2019 for our lead three programs included filing an MAA with the EMA for OTL-200 ahead of schedule, releasing key data sets with respect to OTL-101, OTL-200 and OTL-103, and initiating a clinical trial for OTL-103 in which patients were treated using a cryopreserved formulation.
- **Build a world-leading pipeline, advancing early stage programs into and through the clinic** – We made several advancements to our pipeline, including in-licensing OTL-203 for the treatment of MPS-I, reporting clinical proof-of-concept data for two of our product candidates and submitting a clinical trial application for another product candidate.
- **Build a world-leading chemistry, manufacturing, and controls ("CMC") platform, including manufacturing facility design and implementation of processes for improved transduction efficiency** – We completed the conceptual design of an in-house manufacturing facility in Fremont, California and initiated implementation of select transduction enhancers for certain of our clinical programs.
- **Fund Company growth and operations through mid-2021** – We entered into a credit facility in May 2019 and closed a follow-on public offering in June 2019, which extended our cash runway into the second half of 2021.

During a series of meetings in December 2019 and January 2020, the Compensation Committee evaluated our achievement of the 2019 corporate objectives and each executive director's individual performance. Based on our 2019 results, the Compensation Committee determined that our corporate performance was 140% of target.

The table below sets forth the 2019 annual base salaries, target annual cash bonuses, relative weighting of corporate and individual performance, and the 2019 annual cash bonuses earned by our executive director's.

| Executive Director | 2019 Annual Base salary (\$) | Target Annual Cash Bonus (% of annual base salary) | Corporate performance | | | Individual Performance | | | Annual Cash Bonus (%) | Annual Cash Bonus (\$) |
|--------------------|------------------------------|--|-----------------------|-----------------------|-------------------|------------------------|-----------------------|-------------------|-----------------------|------------------------|
| | | | Weighting (%) | Outcome (% of salary) | Cash outcome (\$) | Weighting (%) | Outcome (% of salary) | Cash outcome (\$) | | |
| Mark Rothera | \$527,440 | 50% | 100% | 140% | \$369,208 | – | – | – | 70% | \$369,208 |
| Bobby Gaspar | \$344,3481 | 35% | 70% | 140% | \$118,111 | 30% | 155% | \$56,042 | 51% | \$174,154 |

1 Mr. Gaspar's base salary and bonus are paid in GBP (£) and awards have been translated into USD at a rate of £1.00 = \$1.3118, which was the prevailing rate as of 31 December 2019.

DIRECTORS' REMUNERATION REPORT

continued

Share Option Incentive Plan

Awards granted to Executive Directors in 2020

In January 2020, the CSO was granted share options. Additionally, upon his promotion, Bobby Gaspar was granted PSUs and share options as follows (in thousands, except share and per share amounts):

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

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

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

- (1) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the vesting commencement date of 2 January 2020.
- (2) Bobby Gaspar received a one-time grant of 195,000 PSUs, effective 1 April 2020. This PSU award vests as follows: 1/3 of the PSUs will vest on each of the first three of specific clinical and regulatory milestones achieved, subject to Bobby Gaspar remaining an employee of the Company on the date of achievement and provided that in each case the milestone is achieved on or before 2 January 2024.
- (3) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the vesting commencement date of 1 April 2020.

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

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

| Executive Director | Form of Award | Date of Grant | Shares Covered | Exercise Price | Face Value at Date of Grant | Fair Value at Date of Grant | Expiry Date | Vest Terms | Vested | Exercised | Value realized at exercise | Unexercised |
|--------------------|---------------|---------------|----------------|----------------|-----------------------------|-----------------------------|-------------|------------|--------|-----------|----------------------------|-------------|
| Mark Rothera | FMV options* | 16 Jan 2019 | 415,000 | \$12.54 | \$5,204 | \$3,330 | 15 Jan 2029 | (1) | 95,104 | Nil | N/A | 415,000 |
| Bobby Gaspar | FMV options* | 16 Jan 2019 | 50,000 | \$12.54 | \$627 | \$401 | 15 Jan 2029 | (1) | 11,458 | Nil | N/A | 50,000 |
| Bobby Gaspar | PSU | 16 Jan 2019 | 18,750 | N/A | \$235 | \$235** | 31 Dec 2021 | (2) | Nil | N/A | N/A | N/A |

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

** The fair value on date of grant for the PSU is based on the market price on the date of grant. None of the performance conditions, as described below, have been deemed probable and none have vested as of 31 December 2019.

DIRECTORS' REMUNERATION REPORT

continued

- (1) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the date of grant.
- (2) In January 2019, PSUs were granted to further incentivise the executive team towards meeting longer-term performance milestones and in consideration of completing our follow on offering in 2019. The PSUs granted have a three-year performance period of 1 January 2019 to 31 December 2021 and vest as to 1/3 of the award with vesting linked to the achievement of three specific regulatory and research and development milestones and one market condition based upon the volume weighted-average price ("VWAP") of the Company's ADSs for a certain period. The award becomes fully vested upon achievement of three of the four performance conditions. None of the milestones were deemed probable as of 31 December 2019.

During the year ended 2019, Mark Rothera exercised 30,000 share options that were granted in 2017 with an exercise price of \$2.44 per share. The value realized on exercise was \$372,176.

Awards granted to Executive Directors between 1 January 2018 and 31 December 2018 (audited)

The CEO and CSO received the following share option awards during the financial year from 1 January 2018 through 31 December 2018 prior to our listing as a public company, as set forth in the table below (in thousands, except share and per share amounts):

| Executive Director | Form of Award | Date of Grant | Shares Covered | Exercise Price | Face Value at Date of Grant | Fair Value at Date of Grant | Expiry Date | Vest Terms | Vested | Exercised | Value realized at exercise | Unexercised |
|--------------------|-----------------------|---------------|----------------|----------------|-----------------------------|-----------------------------|-------------|------------|---------|-----------|----------------------------|-------------|
| Mark Rothera | FMV Options* | 7 Feb 2018 | 436,686 | \$2.44 | \$1,064 | \$672 | 6 Feb 2028 | (1) | 200,148 | Nil | N/A | 436,686 |
| Mark Rothera | FMV Options* | 13 Sep 2018 | 410,289 | \$9.06 | \$3,717 | \$2,281 | 12 Sep 2028 | (2) | 128,222 | Nil | N/A | 410,289 |
| Mark Rothera | PSU | 15 Nov 2018 | 219,922 | N/A | \$3,703 | \$3,703** | 31 Dec 2021 | (3) | Nil | N/A | N/A | N/A |
| Bobby Gaspar | Nominal value options | 7 Feb 2018 | 40,015 | £0.00002 | \$98 | \$98 | 6 Feb 2028 | (2) | 18,340 | Nil | N/A | 40,015 |
| Bobby Gaspar | Nominal value options | 13 Sep 2018 | 96,420 | £0.00002 | \$873 | \$873 | 12 Sep 2028 | (1) | 30,131 | Nil | N/A | 96,420 |

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

** The fair value on date of grant for the PSU is based on the market price on the date of grant. None of the performance conditions, as described below, have been deemed probable and none have vested as of 31 December 2018.

- (1) The options vest, and become exercisable, over a four-year period, 25% one year from the grant date, and 36 equal monthly vesting periods thereafter.
- (2) The options vest, and become exercisable, over a four-year period on a monthly basis commencing upon the one-month anniversary of the grant date.
- (3) One third of the award will vest on occurrence of each of the first three of four milestone events, provided that in each case the milestone is achieved on or before 31 December 2021. These milestone events are linked to certain regulatory and research and development milestones. The market value on the date of grant was \$16.84 per share. None of the milestones were deemed to be probable at the time of grant and at 31 December 2018.

DIRECTORS' REMUNERATION REPORT

continued

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

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

| Executive Director | Form of Award | Date of Grant | Shares Covered | Exercise Price | Face Value at Date of Grant | Fair Value at Date of Grant | Expiry Date | Vest Terms | Vested | Exercised | Value realized at exercise | Unexercised |
|--------------------|---------------|----------------|----------------|----------------|-----------------------------|-----------------------------|----------------|------------|--------|-----------|----------------------------|-------------|
| Joanne Beck | FMV Options* | 26 June 2019 | 35,000 | \$13.20 | \$462 | \$287 | 25 Jun 2029 | (1) | Nil | N/A | N/A | 35,000 |
| Marc Dunoyer | FMV Options* | 26 June 2019 | 35,000 | \$13.20 | \$462 | \$287 | 25 June 2029 | (1) | Nil | N/A | N/A | 35,000 |
| James Geraghty | FMV Options* | 26 June 2019 | 35,000 | \$13.20 | \$462 | \$287 | 25 June 2029 | (1) | Nil | N/A | N/A | 35,000 |
| Charles Rowland | FMV Options* | 26 June 2019 | 35,000 | \$13.20 | \$462 | \$287 | 25 June 2029 | (1) | Nil | N/A | N/A | 35,000 |
| Alicia Secor | FMV Options* | 26 June 2019 | 35,000 | \$13.20 | \$462 | \$287 | 25 June 2029 | (1) | Nil | N/A | N/A | 35,000 |
| Hong Fang Song | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Jon Ellis | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| John Curnutte | FMV Options* | 30 August 2019 | 50,000 | \$14.80 | \$740 | \$449 | 29 August 2029 | (2) | 6,944 | Nil | N/A | 50,000 |

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

(1) The options vest, and become exercisable, 33% after one year and 24 equal monthly vesting period thereafter.

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

Jon Ellis received no option grants during the year.

Awards granted to Non-Executive directors in 2018 (audited)

In 2018, Non-executive directors received the following option awards, each vesting based on continued employment only (in thousands, except share and per share amounts):

| Executive Director | Form of Award | Date of Grant | Shares Covered | Exercise Price | Face Value at Date of Grant | Fair Value at Date of Grant | Expiry Date | Vest Terms | Vested | Exercised | Value realized at exercise | Unexercised |
|--------------------|---------------------------|---------------|----------------|----------------|-----------------------------|-----------------------------|-------------|------------|---------|-----------|----------------------------|-------------|
| Joanne Beck | Fair market value options | 21 Jul 2018 | 80,030 | \$7.10 | \$568 | \$353 | 20 Jul 2028 | (1) | 39,815 | Nil | N/A | 80,030 |
| Marc Dunoyer | Nominal value options | 12 Jun 2018 | 80,030 | £0.00002 | \$521 | \$521 | 11 Jun 2028 | (1) | 39,815 | Nil | N/A | 80,030 |
| James Geraghty | Fair market value options | 12 Jun 2018 | 320,120 | \$4.74 | \$1,517 | \$1,450 | 11 Jun 2028 | (1) | 177,133 | Nil | N/A | 320,120 |
| Charles Rowland | Fair market value options | 12 Jun 2018 | 80,030 | \$4.74 | \$379 | \$362 | 11 Jun 2028 | (1) | 39,815 | Nil | N/A | 80,030 |
| Alicia Secor | Fair market value options | 7 Dec 2018 | 50,000 | \$15.09 | \$754 | \$436 | 6 Dec 2028 | (1) | 16,500 | Nil | N/A | 50,000 |

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

(1) The options vest, and become exercisable, over a three-year period, 33% one year from the grant date, and 24 equal monthly vesting periods thereafter.

Jon Ellis received no option grants during the year.

DIRECTORS' REMUNERATION REPORT

continued

Payments to former Directors and for loss of office (audited)

No payments were made to former Directors of the Company or in relation to loss of office during the year.

External directorships

The Executive Directors do not currently hold any outside directorships.

Statement of Directors' shareholding and share interests (audited)

The share interests of each Director as at 31 December 2019 (together with interests held by his or her connected persons) are set out in the table below.

| | Beneficially owned shares as at 31 December 2019 | Shares | | Vested but unexercised | Share Options | | |
|--------------------------------|---|--|---|---------------------------|--|---|--|
| | | Unvested without performance conditions | Unvested with performance conditions | | Unvested without performance conditions | Unvested with performance conditions | |
| Executive Directors | | | | | | | |
| Mark Rothera | 103,796 | – | 219,922 | 1,279,245 | 1,527,428 | – | |
| Bobby Gaspar | 352,319 | – | 18,750 | 637,599 | 151,624 | – | |
| Non-Executive Directors | | | | | | | |
| Joanne Beck | 9,294 | – | – | 39,815 | 75,215 | – | |
| John Curnutte | – | – | – | – | 50,000 | – | |
| Marc Dunoyer | 37,179 | – | – | 39,815 | 75,215 | – | |
| Jon Ellis | – | – | – | – | – | – | |
| James Geraghty | 44,391 | – | – | 177,133 | 177,987 | – | |
| Charles Rowland | 12,294 | – | – | 39,815 | 75,215 | – | |
| Alicia Secor | – | – | – | 68,500 | 16,500 | – | |
| Hong Fang Song | – | – | – | – | – | – | |

The share interests of each Director as at 31 December 2018 (together with interests held by his or her connected persons) are set out in the table below.

| | Beneficially owned shares as at 31 December 2018 | Shares | | Vested but unexercised | Share Options | | |
|--------------------------------|---|--|---|---------------------------|--|---|--|
| | | Unvested without performance conditions | Unvested with performance conditions | | Unvested without performance conditions | Unvested with performance conditions | |
| Executive Directors | | | | | | | |
| Mark Rothera | 90,304 | – | 219,922 | 517,740 | 1,903,933 | – | |
| Bobby Gaspar | 417,319 | – | – | 433,000 | 306,223 | – | |
| Non-Executive Directors | | | | | | | |
| Joanne Beck | 9,294 | – | – | – | 80,030 | – | |
| Marc Dunoyer | 37,179 | – | – | – | 80,030 | – | |
| Jon Ellis | – | – | – | – | – | – | |
| James Geraghty | 44,391 | – | – | – | 320,120 | – | |
| Charles Rowland | 12,294 | – | – | – | 80,030 | – | |
| Alicia Secor | – | – | – | – | 50,000 | – | |
| Hong Fang Song | – | – | – | – | – | – | |

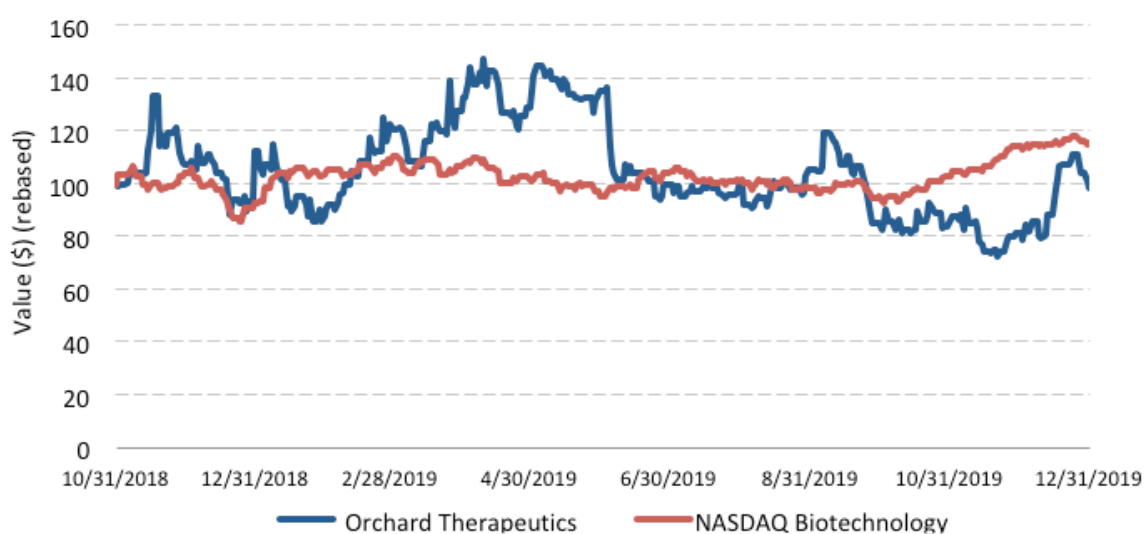
DIRECTORS' REMUNERATION REPORT

continued

Performance graph and table

The chart below shows the Company's Total Shareholder Return (TSR) performance compared with that of the NASDAQ Biotechnology Index over the period from the date of the Company's admission to 31 December 2019. The NASDAQ Biotechnology Index has been chosen as an appropriate comparator as it is the index of which the Company is a constituent. TSR is defined as the return on investment obtained from holding a company's shares over a period. It includes dividends paid, the change in the capital value of the shares and any other payments made to or by shareholders within the period.

Source: FactSet



This graph shows the value, by 31 December 2019, of \$100 invested in Orchard Therapeutics on 31 October 2018 at the IPO price of \$14, compared with the value of \$100 invested in the NASDAQ Biotechnology Index.

The other points plotted are the values at each intervening day.

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. Figures from 2018 were calculated on the accrual basis of accounting for the 2 months since listing from 31 October 2018 to 31 December 2018:

| Chief Executive Officer | 2018 | 2019 |
|---|-------|---------|
| Total remuneration (\$000) | \$555 | \$3,904 |
| Actual bonus (% of the maximum) | N/A | 44%* |
| SOIP PSUs vesting (% of the maximum) ** | N/A | N/A |

* Calculated as actual bonus paid in year over the maximum of two times 80% at target, i.e. 160% of salary

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

DIRECTORS' REMUNERATION REPORT

continued

Percentage change in remuneration of the Chief Executive Officer

The year on year movement to 31 December 2019 of CEO pay versus that of employees is disclosed in the table below.

| | CEO % change* | Employees % change |
|---------------|------------------|-----------------------|
| Salary | 3% | 10% |
| Benefits* | (25%) | 13% |
| Annual bonus* | 23% | 2% |

* 2018 data annualised. The percentage change noted in the table above has been based on US employees, as our CEO is based in the United States.

Relative importance of spend on pay

The table below illustrates the Company's expenditure on pay by the Group in comparison to research and development expenses.

| | 2018 | 2019 | % change |
|--|----------|-----------|----------|
| Research and development expenses ¹ | \$71,712 | \$117,363 | 64% |
| Total employee pay expenditure (\$'000)* | \$35,265 | \$69,486 | 97% |

1. The effects of a one-time in-process research and development charge in the amount of \$133,601 has been excluded from 2018 research and development expenses.
2. 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 \$19,424k and \$6,766k in non-cash share-based compensation expense for 2019 and 2018 respectively.

Statement of implementation of remuneration policy in 2020

Annual base salary

| | Base salary 2019 | Base salary ² 2020 |
|----------------------------|---------------------|----------------------------------|
| Executive Directors | | |
| Mark Rothera | \$527,440 | \$543,300 |
| Bobby Gaspar ¹ | £262,500 | £338,500 |
| Bobby Gaspar ³ | – | £440,000 |

1. Bobby Gaspar's salary is pro-rated for 4 days a week.
2. Effective from 1 January 2020 unless stated otherwise
3. Promoted to CEO effective 18 March 2020; salary applies from that date and is for 5 days a week.

Benefits and pension

In 2020, Executive Directors are eligible for the same benefits (such as health insurance and pension) as provided to all employees in the jurisdiction in which they reside. Pension contributions for Executive Directors are up to 6% of base salary.

DIRECTORS' REMUNERATION REPORT

continued

Bonus

The CEO will be entitled to a target bonus of 50% of base salary, and the CSO will be entitled to a target bonus of 40% of base salary in 2020, with final payout up to 150% of target bonus. Upon his promotion to CEO, Bobby Gaspar's target annual bonus will be increased to 60%, with a maximum of up to 150% of target bonus.

These 2020 targets and maxima have been set within the overall Directors' Remuneration Policy maximum of twice the maximum target of 80% of salary. The bonus will be paid in cash and subject to the achievement of a number of strategic objectives determined by the Committee.

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

Share Option Incentive Plan (SOIP)

In January 2020, the CSO was granted 200,000 share options in the Company at a strike price of \$13.58 per share, based on the closing price of the Company's ADSs on the Nasdaq Global Select Market on 2 January 2020. The share options will expire 10 years from the date of grant. The share options vest monthly over a 4-year period and contain no performance conditions.

Upon his promotion to CEO, Bobby Gaspar was granted an option to purchase 300,000 of the Company's ordinary shares, effective 1 April 2020 with an exercise price of \$7.05 per share. The foregoing options will vest in equal monthly installments over four years commencing on the date of grant. In addition, Dr. Gaspar received a one-time grant of 195,000 PSUs, effective 1 April 2020. This PSU 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 Company through 2 January 2024. The milestones relate to achievement of specific clinical and regulatory milestones: completing pre-clinical proof-of-concept for non-rare disease indications, submitting an investigational new drug or investigational medicinal product dossier for a rare disease indication, and implementing either a transduction enhancer into a clinical program or developing stable cell line technology that can be used in a clinical trial.

The newly appointed Non-Executive Director, Dr. Steven Altschuler, was granted an option to purchase 50,000 ordinary shares of the Company with an exercise price equal to the closing price of the Company's ADSs on the Nasdaq Global Select Market on 3 February 2020. The shares subject to the option will vest in equal monthly installments over a three-year period commencing on the date of grant. Dr. Altschuler will be eligible to receive an annual stock option grant as well as annual cash retainers and supplementary fees according to Company policy as described below.

DIRECTORS' REMUNERATION REPORT

continued

Non-Executive Directors' fees

Non-Executive Directors will receive the following annual fees for 2020, which will be paid in cash, as follows:

| | Fee (effective from 1 January 2020) In \$'000 | 2019 Fee in \$'000 |
|--|--|---------------------------|
| Base fee: | | |
| Board Chair | \$85 | \$75 |
| Board Member | \$45 | \$35 |
| Additional fees: | | |
| Audit Committee Chair | \$18 | \$15 |
| Audit Committee Member | \$9 | \$7.5 |
| Compensation Committee Chair | \$15 | \$10 |
| Compensation Committee Member | \$7.5 | \$5 |
| Nominating and Corporate Governance Committee Chair | \$10 | \$8 |
| Nominating and Corporate Governance Committee Member | \$5 | \$4 |
| Science and Technology Committee Chair | \$10 | \$18 |
| Science and Technology Committee Member | \$5 | \$4 |

The Company provides an initial, one-time equity award of 50,000 stock options to each new Non Executive Director upon his or her election to our board of directors. Under normal circumstances, initial share awards vest monthly over three years. The Company intends to provide an annual equity incentive award of 35,000 stock options to each Non-Executive Director at the AGM. Options awarded annually will usually vest upon the earlier to occur of the first anniversary of the date of grant or the date of the next annual general meeting.

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

Jon Ellis and Hong Fang Song do not receive fees for their services on the Board.

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

On behalf of the Board

Charles Rowland, Jr.

Chair of the Compensation Committee

[9] April 2020

ORCHARD THERAPEUTICS PLC
UK STATUTORY FINANCIAL STATEMENTS
31 December 2019

Registered Number: 11494381

Parent Company Balance Sheet

at 31 December 2019

| | NOTE | 2019 \$'000 | 2018 \$'000 |
|--|------|----------------|----------------|
| NON-CURRENT ASSETS | | | |
| Investment in subsidiaries | 2 | 844,904 | 809,884 |
| CURRENT ASSETS | | | |
| Debtors | 3 | 122,283 | 324 |
| Prepaid expenses and other deferred costs | 4 | 308 | 1,421 |
| Marketable securities at fair value through other comprehensive income | 5 | 234,596 | – |
| Cash and cash equivalents | | 9,365 | 207,042 |
| CURRENT LIABILITIES | | | |
| Creditors – amounts falling due within one year | 6 | (1,837) | (3,314) |
| NET CURRENT ASSETS | | 364,715 | 205,473 |
| TOTAL ASSETS LESS CURRENT LIABILITIES | | 1,206,619 | 1,015,357 |
| Creditors – amounts falling due after more than one year | 7 | (24,699) | – |
| NET ASSETS | | 1,184,920 | 1,015,357 |
| CAPITAL AND RESERVES | | | |
| Share capital | 8 | 12,321 | 10,914 |
| Share premium | | 334,706 | 203,140 |
| Share compensation reserve | | 74,233 | 34,943 |
| Other comprehensive income | | 218 | – |
| Retained Earnings | | 763,442 | 766,360 |
| TOTAL EQUITY | | 1,184,920 | 1,015,357 |

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

The company has elected to take the exemption under section 408 of the Companies Act of 2006 from presenting the company statement of comprehensive income. The company loss for the period ended 31 December 2019 was \$2,918 (2018: profit of \$285).

The parent company financial statements on pages 56-65 were approved by the Board of Directors on [9] April 2020 and were signed on its behalf by:

Bobby Gaspar

Director

[9] April 2020

Registered number: 11494381

Parent Company Statement of Changes in Equity

for the period ended 31 December 2019

| | Shares | Share Capital \$'000 | Share Premium \$'000 | Share Compen- sation Reserve \$'000 | Other Compre- hensive Income \$'000 | Retained Earnings \$'000 | Total \$'000 |
|--|-------------------|----------------------------|----------------------------|---|---|--------------------------------|------------------|
| At 1 August 2018 (incorporation) | 1 | – | – | – | – | – | – |
| Issue of shares in consideration for the transfer of OTL on 19 October 2018 | 69,761,984 | 774,941 | – | – | – | – | 774,941 |
| Reduction of capital on 26 October 2018 | – | (766,075) | – | – | – | 766,075 | – |
| IPO proceeds | 16,103,572 | 2,048 | 223,403 | – | – | – | 225,451 |
| Underwriter and issuance costs | – | – | (20,263) | – | – | – | (20,263) |
| Share-based compensation | – | – | – | 34,943 | – | – | 34,943 |
| Profit for the period | – | – | – | – | – | 285 | 285 |
| Balance at 31 December 2018 | 85,865,557 | 10,914 | 203,140 | 34,943 | – | 766,360 | 1,015,357 |
| Follow-on offering proceeds | 9,725,268 | 1,233 | 129,036 | – | – | – | 130,269 |
| Underwriter and issuance costs | – | – | (605) | – | – | – | (605) |
| Issue of shares under employee equity plans | 1,332,904 | 174 | 3,135 | – | – | – | 3,309 |
| Share-based compensation | – | – | – | 39,290 | – | – | 39,290 |
| Unrealized gain on marketable securities | – | – | – | – | 218 | – | 218 |
| Loss for the period | – | – | – | – | – | (2,918) | (2,918) |
| Balance at 31 December 2019 | 96,923,729 | 12,321 | 334,706 | 74,233 | 218 | 763,442 | 1,184,920 |

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

Notes to the Parent Company Financial Statements

1. COMPANY ACCOUNTING POLICIES

BASIS OF PRESENTATION AND ACCOUNTING PRINCIPLES

Orchard Therapeutics plc (the “Company”) and its subsidiaries (the “Group” or “Orchard”) is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. The Group’s ex vivo autologous gene therapy approach utilizes genetically-modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Group is advancing seven clinical-stage programs across multiple therapeutic areas, including inherited neurometabolic disorders, primary immune deficiencies and blood disorders, where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

The Company is a public limited company limited by shares, incorporated pursuant to the laws of England and Wales. Our registered office is located at 108 Cannon Street, London, EC4N 6EU, United Kingdom. Orchard Therapeutics plc was originally incorporated under the laws of England and Wales in August 2018 to become a holding company for Orchard Therapeutics Limited.

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

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

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

- the requirements of Section 7 Statement of Cash Flows;
- the requirements of Section 3 Financial Statement Presentation paragraph 3.17(d);
- the requirements of Section 11 Financial Instruments paragraphs 11.41(b), 11.41(c), 11.41(e), 11.41(f), 11.42, 11.44, 11.45, 11.47, 11.48(a)(iii), 11.48(a)(iv), 11.48(b) and 11.48(c);
- the requirements of Section 33 Related Party Disclosures paragraph 33.7;
- the requirements of Section 26 Share-based Payments paragraphs 26.18(b), 26.19-26.21 and 26.23

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

INVESTMENTS

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

Notes to the Parent Company Financial Statements

continued

Foreign Currency

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

GOING CONCERN

The financial statements have been prepared on a going concern basis. The Directors have considered the appropriateness of the going concern basis in the Directors' Report. In addition, the Parent Company acknowledges its responsibility to support its subsidiaries' cash outflows for the foreseeable future. At 31 December 2019 the Group held cash, cash equivalents, and marketable securities of \$325 million, and the Parent Company held cash, cash equivalents, and marketable securities of \$244 million. The directors have prepared a forecast which shows sufficient cash to fund planned research and development, commercial, and operating costs of the Group and the Company into the second half of 2021. The directors have considered the effect of the COVID-19 pandemic on our forecast, and have determined it does not have an effect on our ability to operate as a going concern for at least 12 months from the issuance of these financial statements. Therefore, the directors have at the time of approving the financial statements, a reasonable expectation that the Group and Company have adequate resources to continue in operational existence for the foreseeable future and for a period of at least 12 months from the date of signing these financial statements. Accordingly, the Company continues to adopt the going concern basis of accounting in preparing these financial statements.

SHARE-BASED PAYMENTS

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

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

CASH AND CASH EQUIVALENTS

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

DEBTORS

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

Notes to the Parent Company Financial Statements

continued

MARKETABLE SECURITIES AT FAIR VALUE THROUGH OTHER COMPREHENSIVE INCOME

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

CREDITORS – AMOUNTS FALLING DUE WITHIN ONE YEAR

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

CREDITORS – AMOUNTS FALLING DUE AFTER MORE THAN ONE YEAR

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

SHARE CAPITAL

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

CRITICAL ACCOUNTING ESTIMATES AND JUDGMENTS

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

Investment in subsidiary

The Company has a material investment in subsidiary that arose on the reorganization of the group. The investment is held at cost less accumulated impairment losses. The cost of the investment is determined based on the directors' estimated fair value of the subsidiary at the time of the reorganization, as well as the value associated with share-based payment charges associated with subsidiary employees. The value of the investment at the time of the reorganization was based off of subjective assumptions as to the value of the subsidiary undertaking, and the value of the share-based payment charges is determined by applying the Black-Scholes model, using inputs such as term, volatility, and risk-free rate in order to determine the fair value of the share-based payment charges. At each balance sheet date, the directors must determine if the cost exceeds the fair value of the investment, which requires subjective judgment. For further details, see note 2 of the parent company financials.

Notes to the Parent Company Financial Statements

continued

2. INVESTMENTS

| | Subsidiary undertakings (\$000) |
|---|--|
| As at 1 January 2019 | 809,884 |
| Share-based payments associated with subsidiary employees | 35,020 |
| As at 31 December 2019 | 844,904 |

The share-based payment cost of \$34.9 million and \$35.8 million in 2018 and 2019, respectively, represent share-based payment expense that was pushed down from Orchard Therapeutics plc to Orchard Therapeutics (Europe) Limited and subsidiaries, as a capital injection in the Company's Balance Sheet.

The Company tested the investment assets for impairment as at 31 December 2019 and concluded that the investments were not impaired. The Company has considered the effect of COVID-19 and the macroeconomic environment on the value of the investment after the balance sheet date. The Company notes that the circumstances associated with COVID-19 were not in place as of 31 December 2019, and the impact of the virus is not considered an adjusting post balance sheet event for the purposes of our investments.

SUBSIDIARY UNDERTAKINGS

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

*Held directly by Orchard Therapeutics plc

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

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

Notes to the Parent Company Financial Statements

continued

3. DEBTORS

| | 2019 \$000 | 2018 \$000 |
|--|----------------|---------------|
| Amounts due from subsidiary undertakings | 119,679 | 274 |
| Other receivables | 2,604 | 50 |
| | 122,283 | 324 |

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

4. PREPAID EXPENSES AND OTHER DEFERRED COSTS

| | 2019 \$000 | 2018 \$000 |
|--------------------------|---------------|---------------|
| Deferred financing costs | 307 | – |
| Prepaid expenses | 1 | 1,421 |
| | 308 | 1,421 |

5. MARKETABLE SECURITIES AT FAIR VALUE THROUGH OCI

| | 2019 \$000 | 2018 \$000 |
|----------------------------|----------------|---------------|
| Marketable debt securities | 234,596 | – |
| | 234,596 | – |

6. CREDITORS

– Amounts falling due within one year

| | 2019 \$000 | 2018 \$000 |
|--|---------------|---------------|
| Trade creditors | 323 | 57 |
| Amounts due to subsidiary undertakings | – | 3,186 |
| Accruals | 1,514 | 71 |
| | 1,837 | 3,314 |

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

7. NOTES PAYABLE

In May 2019, the Company entered into a senior term facilities agreement (the “Credit Facility”) with MidCap Financial (Ireland) Limited (“MidCap Financial”), as agent, and additional lenders from time to time (together with MidCap Financial, the “Lenders”), to borrow up to \$75.0 million in term loans in \$25 million increments. To date, the Company has borrowed \$25.0 million under an initial term loan. The remaining \$50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan at the Company’s discretion and upon achievement of certain regulatory milestones and maintenance of \$100 million and \$125 million in cash and cash equivalent investments, respectively. The second term loan of \$25.0 million is available between 30 September 2019 and 31 December 2020. The third term loan of \$25.0 million is available between 1 July 2020 and 30 September 2021. As of 31 December 2019, the Company had met the criteria to draw down the second term loan of \$25.0 million, but this has not been drawn down as at 31 December 2019.

Notes to the Parent Company Financial Statements

continued

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

As of 31 December 2019, notes payables consist of the following:

| | 2019 | 2018 |
|---|---------------|--------------|
| | \$000 | \$000 |
| Notes payable, net of unamortized debt issuance costs | 24,541 | – |
| Accretion related to final payment | 158 | – |
| Notes payable, long term | 24,699 | – |

As of 31 December 2019, estimated future principal payments due are as follows:

| | Aggregate Minimum Payments \$000 |
|--|---|
| Total principal payments due | 25,000 |
| Final payment | 1,125 |
| Total payments | 26,125 |
| Less: unamortized portion of final payment | (967) |
| Less: unamortized debt issuance costs | (459) |
| Notes payable, long term | 24,699 |

Interest expense for the year ended 31 December 2019 was \$1.5 million (2018: nil).

8. SHARE CAPITAL

| | 2019 | 2018 |
|---|---------------|---------------|
| | \$000 | \$000 |
| Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 shares | 12,321 | 10,914 |
| | 12,321 | 10,914 |

As of 31 December 2019 and 2018, 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 2019 and 2018, there were 96,923,729 and 85,865,557 ordinary shares issued and outstanding, respectively. As of 31 December 2019 and 2018, there were a total of 12,216,140 and 10,203,432 share options in respect of ordinary shares outstanding, respectively. In addition, as of 31 December 2019 and 2018, there were 556,422 and 219,922 unvested restricted share units outstanding in respect of ordinary shares outstanding, respectively.

Notes to the Parent Company Financial Statements

continued

In June 2019, the Company completed its follow-on public offering of ADSs. The Company sold an aggregate of 9,725,268 ADSs representing the same number of ordinary shares at a public offering price of \$14.25 per ADS, including a partial exercise by the underwriters of their option to purchase additional ADSs. Net proceeds were \$129.7 million, after deducting underwriting discounts of \$8.3 million, and commissions and offering expenses paid by the Company of \$0.6 million.

During the year ended 31 December 2019, the Company issued 1,209,335 shares as a result of share option exercises, and 123,569 shares from our employee share purchase plan.

As of 31 December 2019 and 2018, 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, 2019, the Company has not declared any dividends.

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

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

9. RELATED PARTY TRANSACTIONS

These are disclosed as part of note 16 in the financial statements on Form 10-K as filed with the SEC. The company has taken advantage of the exemption, under FRS 102 The Financial Reporting Standard applicable in the UK and Republic of Ireland, not to disclose related party transactions with other companies that are wholly owned within the group.

10. ULTIMATE PARENT UNDERTAKING AND CONTROLLING PARTY

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

11. SUBSEQUENT EVENTS

CEO Transition

Effective as of 17 March 2020, Mark Rothera resigned his positions as President and Chief Executive Officer of Orchard Therapeutics plc (the "Company") and as a director of the Company.

On 18 March 2020, the Company announced the appointment of Bobby Gaspar, M.D., Ph.D., as Chief Executive Officer of the Company, effective on 18 March 2020.

Grants of Share Options to Employees and New Directors

On 2 January 2020, the Company granted share options to employees and its former CSO (now CEO) for the purchase of an aggregate of 3,623,295 ordinary shares at an exercise price of \$13.58 per share, split 3,423,295 to employees and 200,000 to the former CSO (now CEO).

On 3 February 2020, the Company granted share options to employees and one new Director for the purchase of an aggregate of 336,567 ordinary shares at an exercise price of \$12.30 per share. Included in this amount is a grant of 50,000 share options to our new Director, Dr. Steven Altschuler, who was appointed to the Board of Directors on 3 February 2020.

Notes to the Parent Company Financial Statements

continued

On 2 March 2020, the Company granted share options to employees and one new Director for the purchase of an aggregate of 126,250 ordinary shares at an exercise price of \$12.05 per share.

On 1 April 2020 the Company granted share options to our CEO and President and Chief Operating Officer for the purchase of an aggregate of 450,000 ordinary shares at an exercise price of \$7.05 per share.

On 1 April 2020, The Company also granted performance-based RSUs to its CEO covering a maximum of 195,000 ordinary shares. These performance-based RSUs will vest, if at all, based upon attainment of certain clinical and regulatory milestones, but must vest by 2 December 2024 or else be forfeited.

COVID-19 Risks and Uncertainties

Since 31 December 2019, a novel strain of coronavirus, now referred to as COVID-19 has continued to spread globally, has been declared a pandemic by the World Health Organization and has spread to over 100 countries, including the United States and United Kingdom. The impact of this pandemic has been and will likely continue to be extensive in many aspects of society, which has resulted in and will likely continue to result in significant disruptions to the global economy, as well as businesses and capital markets around the world.

The Group and the Company is subject to risks associated with the COVID-19 pandemic. In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy, have placed significant restrictions on travel. Limitations on travel and other social distancing measures may have an effect on our clinical activities and regulatory timelines. Travel and stay-at-home orders could adversely affect our contract manufacturers and third-party logistics providers. Shelter-in-place and stay-at-home orders in California has caused the Group and the Company to temporarily suspend construction activities on our planned manufacturing facility in Fremont, California. Commercial activity associated with our EMA-approved gene therapy for ADA-SCID, Strimvelis, has been postponed by the treatment site and scheduled patients are continuing to receive enzyme replacement therapy until treatment with Strimvelis can occur. Any prolonged material disruptions to the Group and the Company's employees, suppliers, contract manufacturers, vendors, or patients could impact our operating results and could lead to impairments. The Group and the Company's ability to access the capital markets could be impacted if disruptions in the capital markets continue. The value of the investment in subsidiaries held by the Company could also be impaired if the recoverable amount of the companies in which an investment is held falls below the carrying value of the total investment.

**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, 2019

OR

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

Commission File Number 001-38722

ORCHARD THERAPEUTICS PLC

(Exact name of Registrant as specified in its Charter)

England and Wales
(State or other jurisdiction of
incorporation or organization)

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

108 Cannon Street
London EC4N 6EU
United Kingdom

(Address of principal executive offices)

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

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

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

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

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

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

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

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

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

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

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

Indicate by check mark whether the Registrant 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 \$0.9 billion.

As of February 14, 2020, the Registrant had 97,068,993 ordinary shares, nominal value £0.10 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive proxy statement for its 2020 Annual General Meeting are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains express or implied forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve substantial risks and uncertainties. In some cases, forward-looking statements may be identified by the words “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “continue,” “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. The forward-looking statements and opinions contained in this Annual Report are based upon information available to our management as of the date of this Annual Report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. Forward-looking statements contained in this Annual Report include, but are not limited to, statements about:

- the timing, progress and results of clinical trials and preclinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the timing, scope or likelihood of regulatory submissions, filings, and approvals;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the size of the patient populations for our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial product, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our commercial product and product candidates, if approved;
- the scalability and commercial viability of our manufacturing methods and processes, including our plans to develop our in-house manufacturing operations;
- the rate and degree of market acceptance and clinical utility of our commercial product and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our commercial product 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 and manufacturers and their ability to perform adequately; 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.

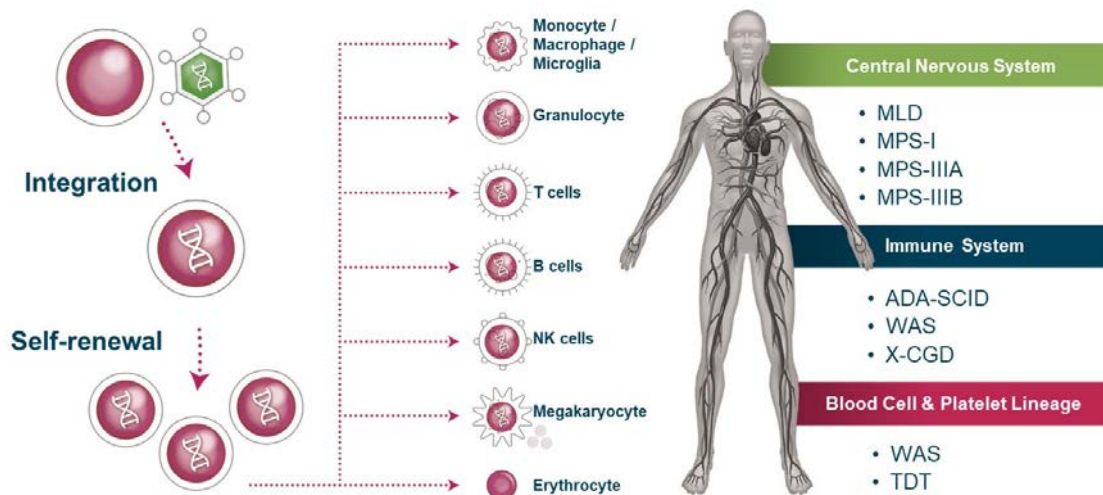
We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of people affected by rare diseases through *ex vivo* autologous hematopoietic stem cell, or HSC, gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous, HSCs into a gene-modified cellular drug product to treat the patient's disease through a single administration. We achieve this outcome by utilizing a lentiviral vector to introduce a functional copy of a missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process, resulting in a drug product that can then be administered to the patient at the bedside.

To date, over 170 patients have been treated with our commercial product and clinical-stage product candidates across seven different diseases, with follow-up periods of more than 18 years following a single administration. We believe the data observed across these programs, in combination with our deep expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide potentially transformative therapies to people suffering from a broad range of diseases.

We are currently focusing our *ex vivo* autologous HSC gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders and blood disorders. Our portfolio includes Strimvelis, our commercial-stage gammaretroviral-based product approved in Europe for the treatment of adenosine deaminase-severe combined immunodeficiency, or ADA-SCID, seven lentiviral-based product candidates in clinical-stage development and several other product candidates in preclinical development. Our three lead clinical programs, OTL-200 for the treatment of metachromatic leukodystrophy, or MLD, OTL-101 for the treatment of ADA-SCID, and OTL-103 for the treatment of Wiskott-Aldrich syndrome, or WAS, have a combined annual incidence rate of between 700 and 1,300 patients in markets around the world where treatments for rare diseases are often reimbursed. We believe the total market opportunity in the disease areas underlying these three programs could be greater than \$1.5 billion annually based on incidence alone. If we take into account prevalent populations of people living with these diseases who could be eligible for our treatments upon receiving marketing approval, our market opportunity could be increased.

For each of our lead product candidates, we are in ongoing discussions with the applicable regulatory authorities with respect to the clinical and other data required for regulatory submissions. We filed a marketing authorization application, or MAA, with the European Medicines Agency, or EMA, for OTL-200 for the treatment of MLD in 2019, and we anticipate filing a biologics license application, or BLA, with the U.S. Food & Drug Administration, or FDA, for OTL-200 for the same indication by 2021. We plan to make additional regulatory submissions over the next two years with the FDA for OTL-101 for the treatment of ADA-SCID and with the FDA and EMA for OTL-103 for the treatment of WAS.

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.



We have a broad and advanced portfolio of commercial- and development-stage products and product candidates. Our neurometabolic disorders franchise consists of one advanced registrational clinical program, OTL-200 for MLD, two clinical proof of concept-stage programs, OTL-203 for mucopolysaccharidosis type I, or MPS-I, and OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, and a preclinical program, OTL-202 for mucopolysaccharidosis type IIIB, or MPS-IIIB. Our primary immune deficiencies franchise consists of our commercial program approved in Europe, Strimvelis for ADA-SCID, two advanced registrational clinical programs, OTL-101 for ADA-SCID and OTL-103 for WAS, and one clinical proof of concept-stage program, OTL-102 for X-linked chronic granulomatous disease, or X-CGD. Our blood disorders franchise consists of one clinical proof of concept-stage program, OTL-300 for transfusion-dependent beta-thalassemia, or TDT. See “—Our pipeline.”

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare or ultra-rare indications, we believe our clinical programs will generally be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. 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. See “—Our regulatory strategy.”

The diseases we are targeting affect patients around the world, requiring an infrastructure to deliver gene therapies globally. We are therefore building a commercial-scale manufacturing infrastructure and leveraging technologies that will allow us to deliver our gene therapies globally in a fully-integrated manner. In order to meet anticipated demand for our growing pipeline of product candidates and planned product offerings, we are initially 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 Menlo Park, California and in London, UK, and plan to build an integrated facility in Fremont, California to accommodate our expanding process development and create in-house drug product and vector manufacturing capabilities.

Cryopreservation of our gene-modified HSCs is a key component of our strategy to deliver potentially transformative gene therapies to patients worldwide, facilitating both local treatment and local product reimbursement. In anticipation of commercialization, we have developed cryopreserved formulations of our three most advanced product candidates and are collecting supportive clinical data from patients treated with cryopreserved formulations to support the analytical comparability analysis to the fresh cell formulations used in our registrational trials. The registrational trials for all our earlier stage product candidates will be conducted using one of our cryopreserved formulations.

We have global commercial rights to all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including the United States and Europe initially, subject to obtaining the necessary marketing approvals for these jurisdictions. We plan to deploy a focused commercial infrastructure to deliver our product candidates 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.

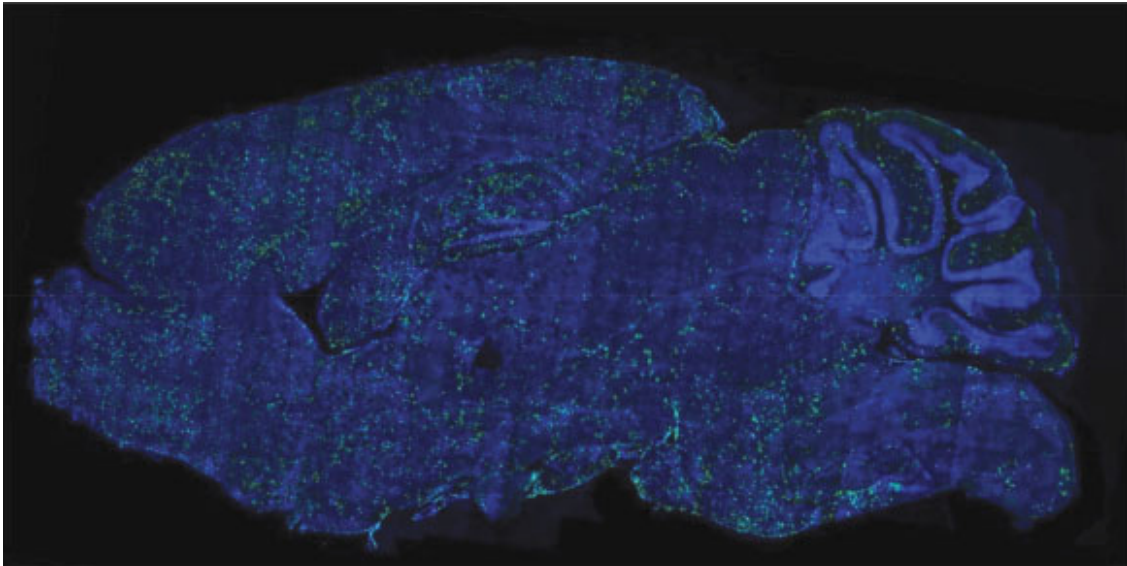
As we continue to develop and expand our portfolio, we believe that the deep experience of our management team and our extensive academic relationships are key strategic strengths. Our management team has extensive experience in rare diseases and in the manufacturing, preclinical and clinical development and commercialization of gene and cell therapies. In addition, we partner with leading academic institutions, 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 for rare diseases.

Our *ex vivo* autologous HSC gene therapy approach

Our *ex vivo* 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. 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. 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.

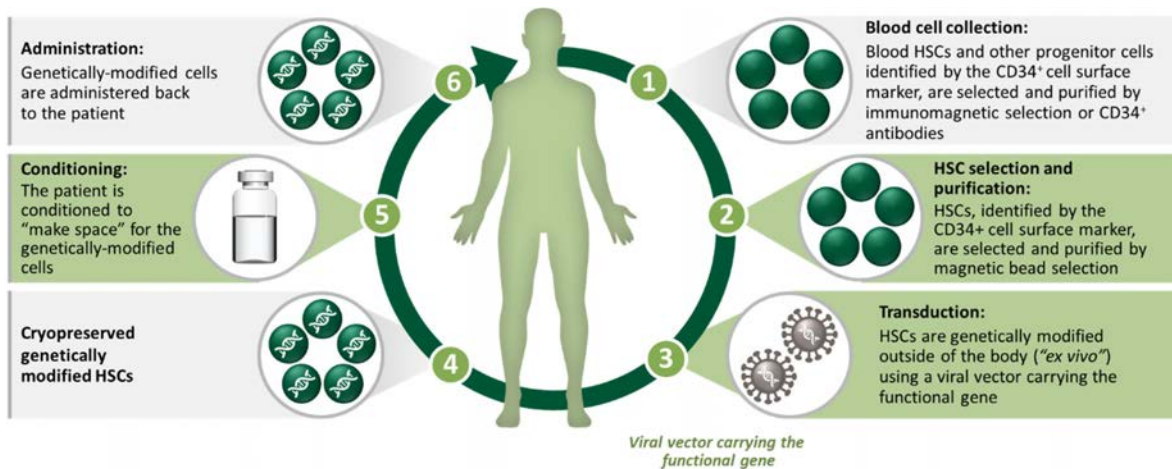
Clinical validation already exists for hematopoietic stem cell transplantation, or HSCT, an approach of treating a patient with a genetic disease with HSCs contributed by a healthy donor individual, thereby using HSCs that contain a functioning copy of the gene of interest. However, this approach has 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 necessarily at 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.

The following discussion is an example of the potential of our *ex vivo* autologous HSC gene therapy approach to deliver genes to different physiological systems. In a preclinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America*, or *PNAS*, a subpopulation of gene-modified HSCs has evidenced the potential to cross the blood-brain barrier, engraft in the brain as microglia and express genes and proteins within the central nervous system. As published in *PNAS*, the image below shows 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. Our OTL-200 program for MLD 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 figure below shows 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 each of our product candidates, our *ex vivo* gene therapy approach utilizes a non-replicating 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. Strimvelis, our commercial-stage product, utilizes a non-replicating gammaretroviral vector.

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



Initial clinical trials conducted using our product candidates utilized a fresh product formulation, resulting in a limited drug product shelf life. We plan to market our current and 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 throughout the world, allowing patients to receive treatment closer to their home. 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 selected third party commercial CDMOs with vector and drug product manufactured at such academic centers.

Initially, we are employing our *ex vivo* autologous HSC gene therapy approach in three franchise areas: primary immune deficiencies, neurometabolic disorders and blood disorders. Data from clinical trials suggest that *ex vivo* autologous HSC gene therapy has the potential to provide well-tolerated, sustainable and improved outcomes over existing standards of care for diseases in these franchise areas. We believe that we can apply our approach beyond our initial target indications to treat an even broader range of diseases.

Our strategy

Our mission is to transform the lives of patients with rare genetic diseases using our *ex vivo* autologous HSC gene therapy approach. We are building a leading, global, fully-integrated gene therapy company focused on serious and life-threatening diseases. To achieve this, we are pursuing the following strategies:

- Advance our seven clinical-stage product candidates towards marketing approvals
- Leverage the power of our therapeutic approach to expand our product pipeline across multiple indications
- Establish end-to-end process development, manufacturing and supply chain capabilities
- Establish a patient-centric, global commercial infrastructure
- Execute a disciplined business development strategy to strengthen our portfolio of product candidates

Our pipeline

Our advanced portfolio of *ex vivo* autologous HSC gene therapies targets serious and life-threatening rare diseases, currently focusing on primary immune deficiencies, neurometabolic disorders and blood disorders. Our primary immune deficiencies franchise consists of our commercial program approved in Europe, Strimvelis for ADA-SCID, two advanced registrational clinical programs, OTL-101 for ADA-SCID and OTL-103 for WAS, and one clinical proof of concept-stage program, OTL-102 for X-CGD. Our neurometabolic disorders franchise consists of one advanced registrational clinical program, OTL-200 for MLD, two clinical proof of concept-stage programs, OTL-203 for MPS-I and OTL-201 for MPS-IIIA, and a preclinical program, OTL-202 for MPS-IIIB. Our blood disorders franchise consists of one clinical proof of concept-stage program, OTL-300 for TDT.

The status of these programs is outlined below:



Gene therapy for treatment of ADA-SCID

Disease overview

Severe combined immunodeficiency, or SCID, is a rare, life-threatening inherited disease of the immune system. ADA-SCID is a specific form of SCID, commonly known as “bubble-baby disease,” caused by mutations in the ADA gene, resulting in a lack of, or minimal, immune system development, which leaves the patient vulnerable to severe and recurrent bacterial, viral and fungal infections. The first symptoms of ADA-SCID typically manifest during infancy with recurrent severe bacterial, viral and fungal infections and overall failure to thrive, and without treatment the condition can be fatal within the first two years of life. The lack of a functional ADA gene in ADA-SCID patients can also lead to neurological deficits involving motor function, deafness, liver dysfunction and eventual failure, and cognitive and behavioral dysfunction.

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

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

Limitations of current therapies

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

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

Our solutions, OTL-101 and Strimvelis for treatment of ADA-SCID

We are developing OTL-101 as an *ex vivo* autologous lentiviral gene therapy to treat patients with ADA-SCID through a single administration. OTL-101 is manufactured from HSCs isolated from the patient's own bone marrow or mobilized peripheral blood that is genetically modified to introduce a functional copy of the ADA gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a mild conditioning regimen.

OTL-101 has been investigated in multiple clinical trials in the United States and Europe. As of January 2020, 66 patients have been treated with a drug product manufactured with the EFS-ADA lentiviral vector, with a maximum follow-up of approximately 8 years post treatment. Based on our ongoing discussions with the FDA, we expect our BLA submission will include data from our the registrational trial being conducted by University of California Los Angeles, or UCLA, of 20 patients treated with a fresh product formulation of OTL-101, supportive data derived from a clinical trial of 10 patients treated with a cryopreserved formulation at UCLA and additional data derived from a clinical trial of 10 patients treated with a fresh product formulation at Great Ormond Street Hospital, or GOSH, as well as any other patients with adequate follow-up at the time of submission. See “—Regulatory Pathway for OTL-101.” The remaining 26 patients treated as of January 2020 represent compassionate use patients or patients for whom we do not have adequate follow-up as of the date of this Annual Report but for which safety data is presented in the summary below. Among the 66 patients treated, four patients, including those treated under compassionate use and additional supportive studies, did not engraft or had to resume ERT and/or receive rescue bone marrow transplant.

In the European Union, our commercial program Strimvelis is available as the only approved gene therapy option for patients with ADA-SCID. The EMA approved Strimvelis in May 2016 for treatment of children with ADA-SCID with no suitable HLA-matched stem cell donor. Strimvelis consists of HSCs transduced with a gammaretroviral vector encoding the human adenosine deaminase cDNA sequence. Strimvelis is available in fresh product formulation at San Raffaele Hospital in Milan, Italy, and has a shelf-life of up to six hours. We plan to continue to make Strimvelis available to eligible patients as we advance OTL-101 as an *ex vivo* autologous lentiviral gene therapy for ADA-SCID.

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

OTL-101 has received orphan drug designation from the FDA and the EMA for the treatment of ADA-SCID and Breakthrough Therapy Designation from the FDA. OTL-101 has also received a Rare Pediatric Disease Designation from the FDA. We expect to initiate a rolling BLA for OTL-101 with the FDA in the first half of 2020 with anticipated completion of the filing within 12 months of initiation.

Registrational, supportive and ongoing additional clinical trials

OTL-101 has been evaluated in a registrational trial conducted by UCLA in the United States using a fresh product formulation and has also been evaluated in a supportive clinical trial at UCLA using a cryopreserved formulation. These trials were initially conducted under an investigator-sponsored investigational new drug application, or IND, to which we hold the license. A fresh product formulation was evaluated in a concurrent additional investigator-sponsored clinical trial conducted by GOSH in Europe. These clinical trials enrolled ADA-SCID patients between one month and 18 years of age who were ineligible for HSCT due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

Registrational trial conducted by UCLA (“UCLA Fresh study”)

Our anticipated rolling BLA submission for OTL-101 will include data from 20 enrolled and treated patients in a registrational trial conducted by UCLA for which follow-up completed in August 2018. Production of the fresh OTL-101 drug product formulation (with bone marrow as the cellular source) used in this clinical trial was performed onsite at UCLA and at the National Institutes of Health, or NIH, for one patient. In this clinical trial, all patients were treated with ERT prior to enrollment and continued ERT until 30 days following their treatment with OTL-101.

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

Overall survival and event-free survival of 100% was observed at 12 months post-treatment, the primary endpoint of the trial. None of the enrolled patients required rescue medication, HSCT, or resumption of ERT. As summarized in the charts below, these patients' data were compared with a historical cohort of ADA-SCID, for which patients 0 to 18 years of age were eligible, who received treatment with allogeneic bone marrow transplant between 2000 and 2016 (n=26). These data were gathered retrospectively from Great Ormond Street Hospital and Duke University Hospital. Comparator populations from this group were ADA-SCID patients without an eligible HLA-matched related donor, patients with an HLA-matched related donor, or MRD, and the complete group.

When comparing the overall survival for the OTL-101 treated patients with the historical control group, OTL-101 treated patients achieved a higher overall survival rate at 24 months (100%) versus the combined group that received allogeneic bone marrow transplant (88%) (95% CI: 69-97%). A confidence interval, or CI, is a range of values in which, statistically, there is a specified level of confidence that the true rate falls within this range. Small sample sizes will yield wider confidence intervals. In this trial, the results indicate that there is a 95% level of confidence that the overall survival rate for OTL-101 at the 24-month timepoint was between 83% and 100%, which we represent as (95% CI: 83%-100%).

OTL-101 (ADA-SCID): Summary of Overall Survival (n=20) at 24 months

| | Overall Survival (95% CI) | Reduction from OTL-101 group (95% CI) |
|---------------------------------|---------------------------------|---|
| OTL-101 pivotal data | 100% (83.16, 100) | - |
| HSCT without MRD | 85% (57.19, 98.22) | 14.29% (-5.40, 42.81) |
| HSCT with MRD | 90.91% (58.72, 99.77) | 9.09% (-9.55, 41.28) |
| All HSCT | 88% (68.78, 97.45) | 12.00% (-5.62, 31.22) |

As summarized in the chart below, event-free survival is defined as survival without resumption of PEG-ADA ERT or need for rescue allogeneic HSCT. Event-free survival in the OTL-101 treatment group was 100% at 24 months. In comparison, event-free survival in the combined allogeneic HSCT group was 56% (95% CI: 34.9-75.6%) at 24 months. For the primary comparator group, who received allogeneic HSCT without a matched related donor, event-free survival rates had differences of 50% (95% CI: 22.71-76.96%) compared to the OTL-101 treated group at 24 months. Because the 95% confidence intervals for the estimates of the difference from the OTL-101 treated group do not include zero, these are statistically meaningful differences between the OTL-101 treated group and the HSCT without a matched related donor comparator group. Similarly, event-free survival rates in the comparator HSCT group that received a matched related donor (the current standard of care) had differences of 36.36% (95% CI: 9.80-69.21%) compared to the OTL-101 treated group at 24 months. Because the 95% confidence intervals for this estimate does not include zero, this also represents a statistically meaningful difference between the OTL-101 treated group and the comparator HSCT with a matched related donor.

OTL-101 (ADA-SCID): Summary of Event-Free Survival (n=20) at 24 months

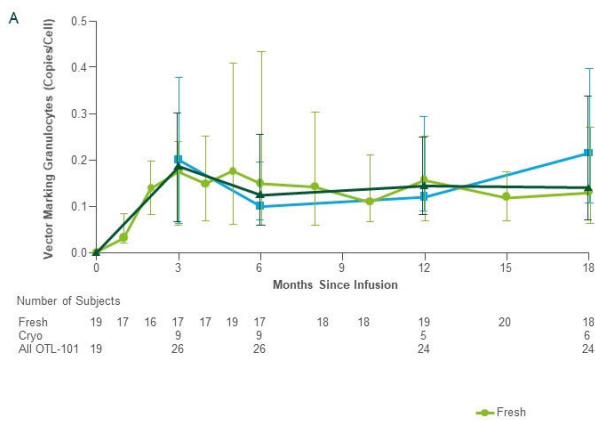
| | Event-Free Survival (95% CI) | Reduction from OTL-101 group (95% CI) |
|---------------------------------|---------------------------------|---|
| OTL-101 pivotal data | 100% (83.16, 100) | - |
| HSCT without MRD | 50.00% (23.04, 76.96) | 50.00% (22.71, 76.96) |
| HSCT with MRD | 63.64% (30.79, 89.07) | 36.36% (9.80, 69.21) |
| All HSCT | 56.00% (34.93, 75.60) | 44.00% (22.78, 65.23) |

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

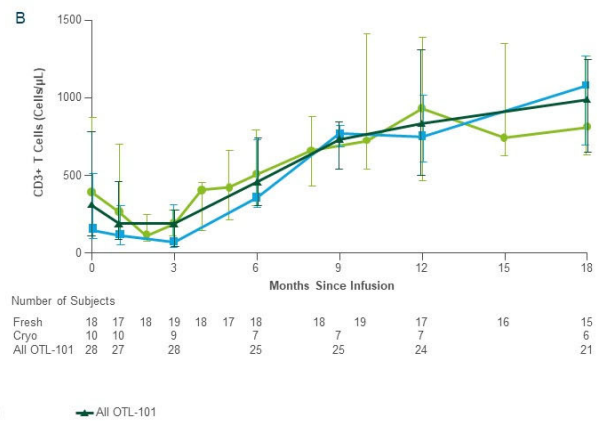
Supportive clinical trial with UCLA (with cryopreserved formulation) (“UCLA Cryo study”)

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

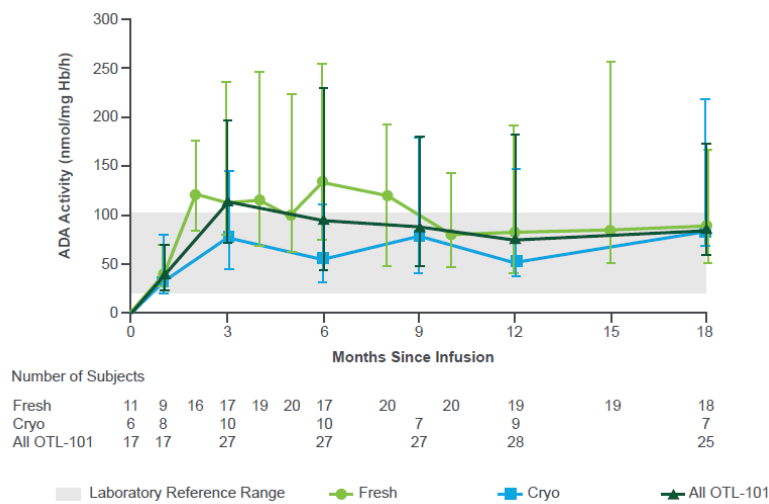
Median VCN in Granulocytes



Median Lymphocyte Counts



Median ADA Activity (Interquartile Range)



We believe this consistency between the UCLA Fresh and UCLA Cryo studies is supportive of ongoing analytical comparability data between the fresh and cryopreserved formulations of OTL-101. We are continuing to evaluate the data from this ongoing trial and will include the data available at the time of submission to support our BLA and MAA submissions.

Additional clinical data from GOSH

In a parallel investigator-sponsored trial being conducted by GOSH, 10 enrolled patients have been treated with fresh product formulation (with bone marrow and mobilized peripheral blood as the cellular source). The drug product used in this clinical trial is produced using the same vector as at UCLA, but with a manufacturing process with minor differences to that for OTL-101. Production of the fresh formulation of the drug product used in this clinical trial was performed onsite at GOSH. In this clinical trial, all patients were being treated with ERT prior to enrollment and all but one patient continued ERT until 30 days following initial treatment with *ex vivo* autologous HSC gene therapy.

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

As of September 2017, overall survival of 100% has been observed at 12 months post treatment in the 10 patients enrolled, and nine patients have achieved event-free survival, with only one patient resuming ERT after 12.2 months due to a failure to engraft. We believe this failure to engraft may in part be attributable to the patient's early discontinuation of ERT prior to treatment in contravention of the trial protocol, but may also relate to other clinical factors. The last study patient has completed their 36-month follow-up but the final study data are not available as of the date of this Annual Report.

There is a second investigator-sponsored trial being conducted by GOSH, aiming to enroll 10 patients treated with cryopreserved product formulation with mobilized peripheral blood as the cellular source. The drug product used in this clinical trial is produced using the same vector and same manufacturing process as the drug product being evaluated at UCLA. Production of the cryopreserved formulation of the drug product used in this clinical trial is performed onsite at GOSH. In this clinical trial, all patients are being treated with ERT prior to enrollment and continue ERT until 30 days following initial treatment with *ex vivo* autologous HSC gene therapy.

The primary goals of this clinical trial are to assess the safety and efficacy of the investigational drug product in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates. As of January 2020, nine patients are alive and no longer being treated with ERT.

OTL-101 program safety

As of August 2019, the data cut-off for the last safety update report, safety data from the 30 patients treated in the registrational and supportive trials (UCLA Fresh and UCLA Cryo, respectively) in the United States indicate that OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis in follow-ups ranging from 17.9 months to 26 months in those who had successful engraftment. A total of 35 serious adverse events, or SAEs, were reported from both the UCLA Fresh and UCLA Cryo studies, of which 1 was assessed by the investigator as being possibly related to treatment due to contamination of OTL-101 protocol treatment or procedures. This SAE was a staphylococcal infection from the patient's transduced bone marrow cells in the UCLA Fresh study. The patient was treated with antibiotics and recovered. The most common SAEs were infections and gastrointestinal disorders. All SAEs resolved with standard treatments, including two cases of immune reconstitution inflammatory syndrome, also assessed as unrelated to OTL-101 by the investigators, and which resolved with corticosteroids. Because follow-up is ongoing, safety data are preliminary and subject to change until closure of both studies. As of the date of this Annual Report, we have not been notified by the investigators of any serious, unexpected and related event, or SUSAR, in either clinical trial.

As of August 2019, the data cut-off for the last safety update report, out of the 3 compassionate use patients treated at UCLA, one with fresh drug product and two with cryopreserved drug product, 5 SAEs were reported and were not deemed to be related to OTL-101. All SAEs resolved with standard of care treatment. Because follow-up is ongoing, safety data are preliminary and subject to change.

In Europe, as of August 2019, the data cut-off for the last safety update report, safety data from the 10 patients treated in the additional clinical trial with GOSH and from the 10 compassionate use patients, indicate that the investigational drug product was generally well-tolerated, with no instances of insertional mutagenesis up to six years post treatment. There were 21 SAEs reported in eight subjects in this additional clinical trial with GOSH, none of which were assessed by the investigator as being possibly related to the protocol treatment, and seven SAEs reported in four patients in the compassionate use program, one of which, a product contamination, was deemed by the investigator as being possibly related to protocol treatment. This SAE was a staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product taken during the transduction procedure at this academic facility. The most common SAEs across this additional clinical trial and compassionate use program were pyrexia, infections and immune system disorders. There were no adverse events, or AEs, or SAEs leading to the withdrawal of patients from the additional clinical trial and compassionate use program. All SAEs resolved with standard of care treatment. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this Annual Report, we have not been notified by the investigator of any SUSAR.

In an ongoing cryopreserved study in the United Kingdom, where eight of ten patients had been treated by the August 2019 data cut-off for the last safety update report, there were eight SAEs reported, none of which were deemed to be related to the drug product. At the same data cut off, in three patients treated under compassionate use with cryopreserved formulation, eleven SAEs have been reported, none of which were deemed to be related to the product. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this Annual Report, we have not been notified by the investigator of any SUSAR.

Regulatory pathway for OTL-101

We are currently planning to initiate the BLA rolling submission for OTL-101 in 2020. We expect that our BLA submission will include clinical data from the registrational trial of 20 patients treated with a fresh product formulation in the UCLA Fresh study, data from the supportive trial of ten patients treated with a cryopreserved formulation in the UCLA Cryo study, additional data from the clinical trial of 10 patients treated with a fresh product formulation at GOSH, and any other patients with adequate follow-up at the time of submission. A global observational long-term follow-up study is now open. Per regulatory requirements, this study is designed to collect safety and efficacy data from ADA-SCID patients previously treated with autologous *ex vivo* gene therapy products based on the EFS-ADA lentiviral vector up to 15 years post gene therapy.

We have completed a final clinical study report for our registrational trial, and we are currently preparing the final clinical report for our supportive clinical trial to support the analytical comparability data between fresh and cryopreserved drug product formulations.

Discussions with FDA on the CMC data package for the BLA have been completed. This data includes analytical comparability between academic and commercial manufacturing processes, vector and drug product process characterization as well as vector and drug product manufacturing state of control and/or process validation. We will initially seek approval of OTL-101 using patient bone marrow as cellular source material and subsequently seek approval for the use of mobilized peripheral blood, as an alternative cellular source material. See *Item 1A. Risk Factors*—“The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission or granting of marketing approval for our product candidates,” “We may be unable to demonstrate comparability between drug product manufactured using HSCs derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product” and “To date, most of the clinical trials for our product candidates were conducted as investigator sponsored clinical trials using drug product manufactured at the academic sites.”

Gene therapy for treatment of MLD

Disease overview

MLD is a rare and rapidly progressive neurometabolic disorder. MLD is caused by a mutation in the *ARSA* gene, leading to a deficiency in the enzyme arylsulfatase A, or ARSA, and the accumulation of sulfatides, resulting in the progressive destruction of myelin in the central and peripheral nervous systems. Prognosis is severe, with continuous neurodegeneration and rapid deterioration of motor functions and cognitive impairment. In late-infantile MLD, the most common and severe form of the disease representing approximately 40-60% of all MLD patients, symptoms are generally first observed before three years of age, and the rate of mortality by five years of age is estimated at 50%. In juvenile MLD, representing approximately 20-35% of all MLD patients, symptoms are generally first observed between three and 16 years of age, and the five-year and ten-year survival rates are 70% and 44%, respectively. In adult MLD, representing approximately 10-25% of all MLD patients, the onset of symptoms generally occurs after 16 years of age. Symptoms often manifest in late-infantile and early-juvenile MLD patients as gait abnormalities and/or missed development milestones. Educational and behavioral symptoms may also accompany gait and motor decline for early-juvenile patients. Adult-onset MLD is often diagnosed through cognitive, behavioral and psychiatric pathologies, such as alcohol or drug use, or difficulty managing emotions resulting in psychiatric evaluation. Adult-onset MLD patients may also demonstrate bewilderment, inappropriate response to their surroundings, paranoia, dementia or auditory hallucinations.

The incidence of MLD is currently estimated at between 1.4 in 100,000 and 1.8 in 100,000 live births per year.

Limitations of current therapies

Currently, there are 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. Given the severity of the disease and the lack of effective treatments, significant burden remains for MLD patients, their caregivers and families, and the healthcare system.

Our solution, OTL-200 for treatment of MLD

We are developing OTL-200 as an *ex vivo* autologous HSC-based gene therapy to treat patients with MLD through a single administration. OTL-200 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood or bone marrow, modified to add a functional ARSA gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen. The gene-modified HSCs have the capacity to migrate to the brain, differentiate into microglia in the brain tissue and secrete ARSA to treat the disease within the central nervous system.

To date, we have treated only late infantile, or LI, and early juvenile, or EJ, patients in our clinical trials of OTL-200. As of January 2020, a total of 36 patients have been treated with OTL-200 drug product, with a maximum follow-up of approximately eight years post treatment, comprised of 20 patients in our registrational trial with a fresh product formulation, seven patients in our supportive study with a cryopreserved formulation and nine patients treated under a compassionate use program with a fresh product formulation. Based on our clinical data to date, we believe OTL-200 has shown the potential to preserve motor function and cognitive development in MLD patients.

We obtained worldwide rights to this program through our asset purchase and license agreement with GSK, or the GSK Agreement. The clinical trials for this program have been conducted under a GSK-sponsored clinical trial authorization, or CTA, which was transferred to us during the third quarter of 2018.

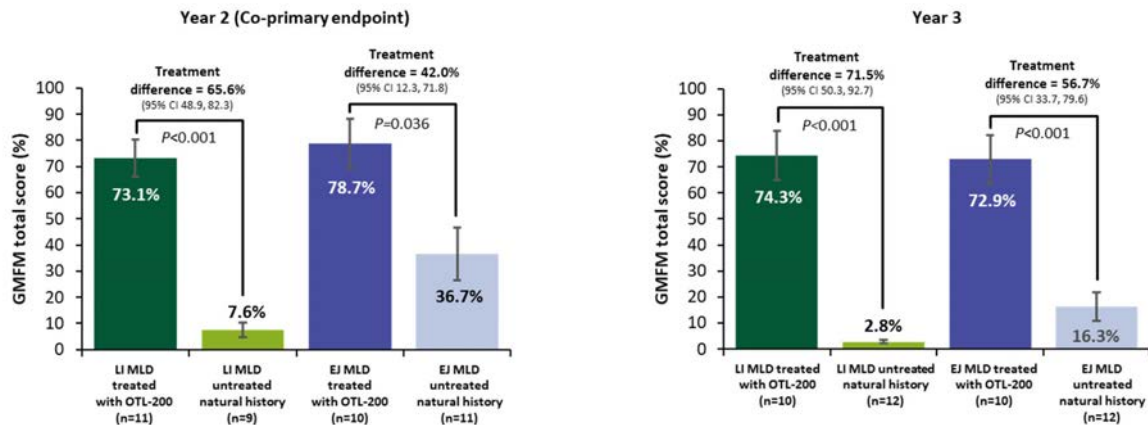
OTL-200 has received orphan drug designation from the FDA and the EMA for the treatment of MLD. OTL-200 has also received Rare Pediatric Disease Designation from the FDA. We submitted an MAA for OTL-200 with the EMA in November 2019, which was validated in December 2019. Accelerated assessment was granted by EMA for the MAA. We plan to submit a BLA with the FDA in late 2020 or early 2021.

Registrational trial

Our MAA submission and anticipated BLA submission for OTL-200 will be supported by data from 29 patients with pre-symptomatic LI MLD, or pre- to early-symptomatic EJ MLD. Twenty of these patients were treated in a registrational trial and nine of the patients were treated under compassionate use programs following the same protocol as the registrational trial at San Raffaele Hospital in Milan, Italy, for which follow-up is ongoing. In this registrational trial, both the late-infantile and early-juvenile patient groups have achieved the co-primary endpoints at 24 months follow-up. Manufacture of the fresh OTL-200 drug product formulation (with bone marrow and/or mobilized peripheral blood as cellular source) was performed by a third-party commercial CDMO.

The primary goals of this clinical trial were to assess the efficacy of OTL-200, as measured by gross motor function and ARSA activity levels in the patients' blood cells 24 months post-treatment, and safety and tolerability of OTL-200 in MLD patients. Secondary goals for this clinical trial included assessment of cognitive function through neuropsychological assessments and instrumental markers of efficacy, such as brain MRI and nerve conduction velocity. The trial also provides for a follow-up period through 8 years' post-treatment.

Presented below are efficacy data from an integrated analysis of all 29 patients treated in this clinical trial and compassionate use programs as of November 2019, the date of the most recent integrated efficacy data report available to us. Motor function was measured in this trial with a GMFM score, which measures a child's ability to perform standard motor tasks including lying and rolling, sitting, crawling and kneeling, standing, and walking, and running and jumping. Healthy children with normal motor development typically reach approximately 100% GMFM score by 3-4 years of age and maintain this score. Following treatment with OTL-200, patients achieved a statistically significant difference on the co-primary endpoint of improvement of >10% of the total GMFM score in treated subjects when compared to the natural history (untreated) cohort at Year 2, and these were maintained through Year 3. At 36 months post-treatment, an average GMFM score of 74.3% was observed in late-infantile patients (n=10) treated in this clinical trial compared to 2.8% in the untreated natural history population. For EJ MLD patients treated in this clinical trial (n=10), an average GMFM score of 72.9% was observed at 36 months post-treatment, compared to 16.3% in the natural history population.



In addition, reconstitution of ARSA activity in the hematopoietic system was observed in OTL-200 treated patients, stabilizing at normal to supra-physiological levels within 3 to 6 months post-treatment. At year 2 post-gene therapy, statistically significant increases in ARSA activity from baseline in total peripheral blood mononuclear (PBMCs) was observed for both the LI (18.7-fold increase; 95% CI: 8.3, 42.2; $p < 0.001$) and EJ (5.7-fold increase; 95% CI: 2.6, 12.4; $p < 0.001$) subgroups, exceeding the pre-specified co-primary endpoint of a significant increase of ≥ 2 standard deviation in ARSA activity in PBMCs at year 2 compared to baseline values. At Year 3 post-gene therapy, the increase in ARSA activity in total PBMCs remained stable for both the LI (37.5-fold increase; 95% CI: 17.7, 79.6; $p < 0.001$) and EJ subgroups (11.2-fold increase; 95% CI: 5.7, 21.9; $p < 0.001$).

Most treated subjects displayed normal acquisition of cognitive developmental skills throughout follow-up. The cognitive age equivalent score is not a single assessment, but a score derived from a number of neuropsychological tests administered according to the chronological age of the patient. Each neuropsychological instrument includes multiple core tests and supplemental subtests that comprise composite scores in specified cognitive areas.

Safety data presented as part of the MAA application showed that of 29 subjects treated as part of a registrational trial or under compassionate use programs, 20 experienced at least one SAE and three subjects died. All three SAEs with a fatal outcome were deemed unrelated to treatment with OTL-200. Two deaths in patients treated after disease onset were attributed to rapid MLD disease progression, and one death in a patient treated before onset of symptoms was attributed to a left hemisphere cerebral ischemic stroke. SAEs that were most frequently reported were gastrointestinal disorders, infections and infestations and nervous system disorders. None of the SAEs were considered by the investigator to be related to OTL-200 but mainly related to myeloablative conditioning with busulfan and to the underlying disease. Overall, the safety findings following treatment with OTL-200 are in line with what would be expected in patients with MLD who have undergone busulfan conditioning and subsequent hematological reconstitution.

Ongoing cryopreservation supportive clinical trial

A cryopreserved formulation of OTL-200 (with bone marrow or mobilized peripheral blood as cellular source) is currently being evaluated in an ongoing clinical trial of pediatric patients with pre-symptomatic LI MLD, or pre- to early-symptomatic EJ MLD in Milan, Italy. Enrollment for this trial is ongoing, with seven patients treated as of January 2020 and up to 10 patients expected to be enrolled.

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

Seven patients have been treated in this trial as of January 2020. All patients tolerated the administration well and for those with enough follow-up post-treatment, preliminary evidence of engraftment and restoration of ARSA activity in peripheral blood to supraphysiological levels and in CSF to normal levels has been shown. To date, four SAEs have been reported in this study, none of which were considered related to the gene therapy.

These clinical data have been used to support the analytical comparability analyses between fresh and cryopreserved formulations that we submitted to EMA as part of our MAA submission.

Regulatory pathway for OTL-200

An MAA was submitted for OTL-200 in November 2019 following preliminary meetings with the EMA and the designated rapporteur and co-rapporteur. The EMA confirmed the validation of the application in December 2019. Of note, EMA has granted accelerated assessment for the review of OTL-200's MAA, potentially reducing the review timeline from 210 to 150 days, assuming no major objections are raised during the MAA assessment or the good clinical practice, or GCP, and current good manufacturing practice, or cGMP, inspections which will be conducted as part of the procedure and not counting clock stops for responses to questions. At this stage we envisage that the MAA for OTL-200 could be granted by the European Commission by the end of 2020, although no assurance can be given that the MAA will be granted by this time, or at all.

In parallel to the European Union registration, we are preparing the BLA for OTL-200. A pre-BLA application has been filed in order to present and discuss the overall clinical development plan as well as key elements of the pharmaceutical package during a meeting to be held at the FDA in the first half of 2020. Depending on the outcome of this meeting, we currently expect to file the BLA by the end of 2020 or early 2021, although no assurance can be given that we will file the BLA by these dates.

See *Item 1A. Risk Factors*—"The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission or granting of marketing approval for our product candidates," and "We may be unable to demonstrate comparability between drug product manufactured using HSCs derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product."

Gene therapy for treatment of WAS

Disease overview

WAS is a rare, life-threatening inherited disease affecting the patient's immune system and platelets leading to recurrent, severe infections and uncontrollable bleeds, which are the leading causes of death in the disease. WAS is referred to as an "X-linked-recessive" disease as it is associated with a genetic defect on the X chromosome. Because it is an X-linked disease, it affects mainly males. Patients with WAS are born with a defect in the gene that produces the WAS protein, or WASP. As a result, they suffer from life-threatening thrombocytopenia and are at risk of severe bleeds, infections, autoimmunity, malignancies and severe eczema. These symptoms require increasingly frequent hospitalizations. The median survival for a patient with WAS is approximately 15 years with patients with early onset WAS generally having a shorter life expectancy.

The incidence of WAS is currently estimated at approximately four in 1 million live male births.

Limitations of current therapies

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

Our solution, OTL-103 for treatment of WAS

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

We obtained worldwide rights to this program through the GSK Agreement. The CTA was transferred to us in August 2018.

As of January 2020, eight patients have been treated with OTL-103 in an ongoing registrational trial and nine patients in an expanded access program, with a maximum follow-up of up to approximately 9 years post-treatment. In addition, a clinical trial using the proposed commercial cryopreserved formulation of OTL-103 was initiated in 2019 and has recruited six subjects five of whom have been treated with a maximum follow up of approximately 8 months.

OTL-103 has received orphan drug designation from the FDA and the EMA for the treatment of WAS. OTL-103 has also received a Rare Pediatric Disease Designation from the FDA. An IND for OTL-103 was opened in 2019 and regenerative medicine advanced therapy, or RMAT, designation was granted. We plan to submit an MAA with the EMA and a BLA with the FDA for OTL-103 for the treatment of WAS in 2021.

Registrational trial

Our anticipated MAA and BLA submissions for OTL-103 will include data from eight currently enrolled patients treated with a fresh product formulation in a registrational trial at San Raffaele Hospital for which follow-up is ongoing. The primary analysis for this registrational trial is prospectively defined to be when all patients have completed three years' follow-up. The eighth and final patient in this trial reached three years' follow-up in late September 2018. Manufacture of the fresh OTL-103 drug product formulation (with bone marrow or mobilized peripheral blood as the cellular source) was performed by a third-party commercial CDMO. Data from the registrational trial will be supported by nine patients dosed in an expanded access program. Based on discussions with the FDA and EMA, we intend to submit data for additional patients treated with the commercial cryopreserved formulation.

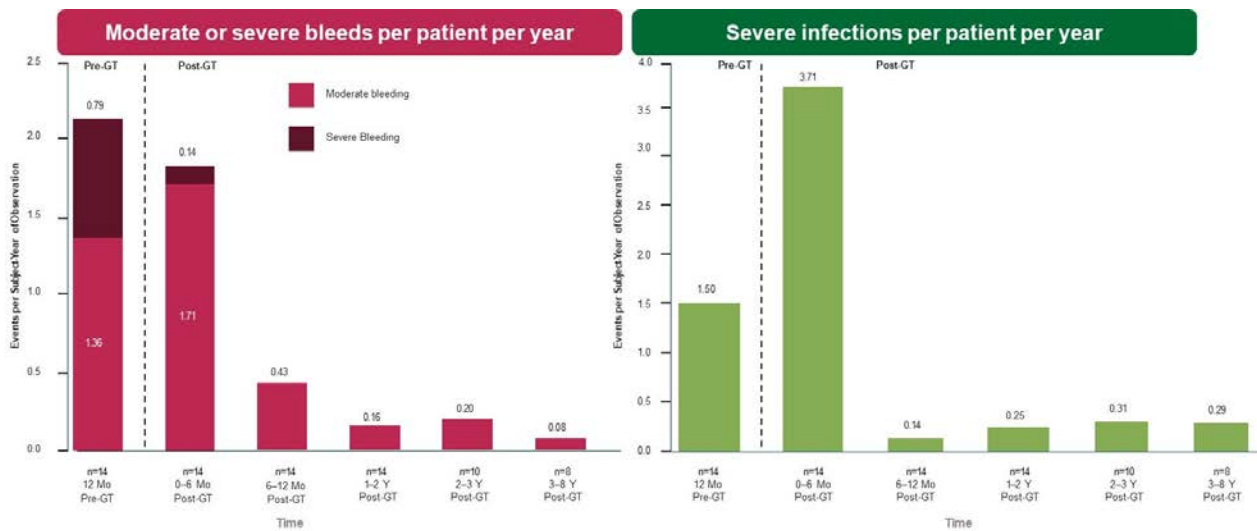
Patients treated in the registrational trial and compassionate use program had a diagnosis of WAS and were ineligible for HSCT treatment due to the absence of an HLA-matched sibling or family member to serve as an allogeneic bone marrow donor. Patients in the study using the cryopreserved formulation also had a diagnosis of WAS and were eligible if no HLA-matched related donor was available.

The primary goals of the registrational clinical trial are to assess the efficacy and safety of OTL-103 in WAS patients, as measured by, for example, improved T-cell function, improved platelet count and overall survival at 36 months. Secondary goals of this clinical trial include reduced bleeding episodes and reduced frequency of severe infections.

The results of an interim analysis of this clinical trial were published in 2019 in *Lancet Haematology* and showed that WASP expression in lymphocytes and platelets was substantially improved compared to baseline by six months and remain constant thereafter. At one-year post-treatment with OTL-103, T-cell counts increased in all seven evaluable patients, as compared to counts prior to treatment, reaching normal values. Because of the increase in T-cells, a reduction in infections was observed in patients post-treatment compared to one year prior to treatment with OTL-103.

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

In patients with at least one year of follow-up ($n=14$), the absence of severe bleeding events and independence from platelet transfusions were observed in all subjects by 9 months of follow-up. Additionally, a reduction in severe infection rate was observed post-treatment.



As of January 2020, the date of the most recent safety report available to us, 100% overall survival has been observed in the eight patients treated in the registrational clinical trial, with a maximum follow-up of up to 9.6 years and a median follow-up of 7.5 years. Safety data from the eight patients treated in the registrational clinical trial indicate OTL-103 was well-tolerated, with no instances of insertional mutagenesis. There were 29 treatment emergent SAEs reported within the trial, none of which were assessed by the investigator as being related to OTL-103. Eight treatment emergent SAEs were reported in six patients in the expanded access program none of which were assessed by the investigator as being related to OTL-103. One patient in the expanded access program died as a consequence of a deterioration in a pre-existing neurological condition. That event was deemed to be unrelated to the product by the investigator. Four treatment emergent SAEs were reported in three patients treated in the Cryo clinical trial using the proposed commercial cryopreserved formulation of OTL-103, and none were assessed by the investigator as being related to OTL-103. Across the program, the most common SAEs were pyrexia and infections. There were no OTL-103 related SAEs leading to the withdrawal of patients from the trial. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this Annual Report, we have not been notified by the investigator of any SUSAR.

Regulatory pathway for OTL-103

In July 2019 the FDA granted RMAT designation for the development of OTL-103. An initial comprehensive multidisciplinary type B meeting with the FDA is expected for early 2020. RMAT designation includes all the benefits of the fast track and breakthrough therapy designation programs, including early interactions with FDA. RMAT programs are intended to facilitate development and review of regenerative medicine therapies that address an unmet medical need in patients with serious conditions. However, RMAT designation is not the same as an approval and does not change the statutory standards for marketing approval. If the FDA determines that later in development of OTL-103 the product no longer meets the qualifying criteria, then the FDA may rescind the RMAT designation.

We are currently in discussions with EMA and FDA to finalize the requirements for our planned MAA and BLA submissions, respectively, for OTL-103 in 2021. We currently expect that our MAA and BLA submissions will include clinical data from a registrational trial of 8 patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, as well as 9 additional patients treated with a fresh product formulation under an expanded access program, and supportive data derived from patients treated at the same clinical site with a cryopreserved formulation. Prior to our BLA and MAA submissions for OTL-103, we will be required to complete a clinical trial report for our registrational trial (with all patients with at least three years follow-up), as well as for our supportive clinical trial with cryopreserved formulation to support analytical comparability between fresh and cryopreserved drug product formulations.

We intend to seek approval of OTL-103 using mobilized peripheral blood as the cellular source. The registration trial included five patients treated with bone marrow as cellular source, two patients with mobilized peripheral blood, and one patient with both. Since then, all patients were treated with mobilized peripheral blood as the cellular source. See *Item 1A. Risk Factors*—“We may be unable to demonstrate comparability between drug product manufactured using HSCs derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product.”

We expect to have additional meetings with EMA and FDA, including a pre-MAA and a pre-BLA meeting, to obtain their concurrence on the appropriate data to support our marketing authorization application. Although we currently expect to complete our MAA and BLA submissions by 2021, our discussions with EMA and FDA are ongoing, and we do not yet have definitive feedback from the EMA and FDA on the scope or adequacy of the requisite data necessary to justify an approval.

Gene therapy for treatment of X-CGD

Disease overview

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

The incidence of X-CGD is currently estimated to be between 2.6 and 10 in 1 million male live births.

Limitations of current therapies

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

Our solution, OTL-102 for treatment of X-CGD

We are developing OTL-102 as an *ex vivo* lentiviral vector-mediated autologous HSC gene therapy to treat patients with X-CGD through a single administration. OTL-102 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood or bone marrow, then modified to add a functional *CYBB* gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen.

OTL-102 is currently being investigated in ongoing investigator-sponsored clinical trials in the United States and in Europe and has evidenced sustained *CYBB* expression for over two years in six patients to date, with a follow-up of up to three years post-treatment in three patients.

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

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

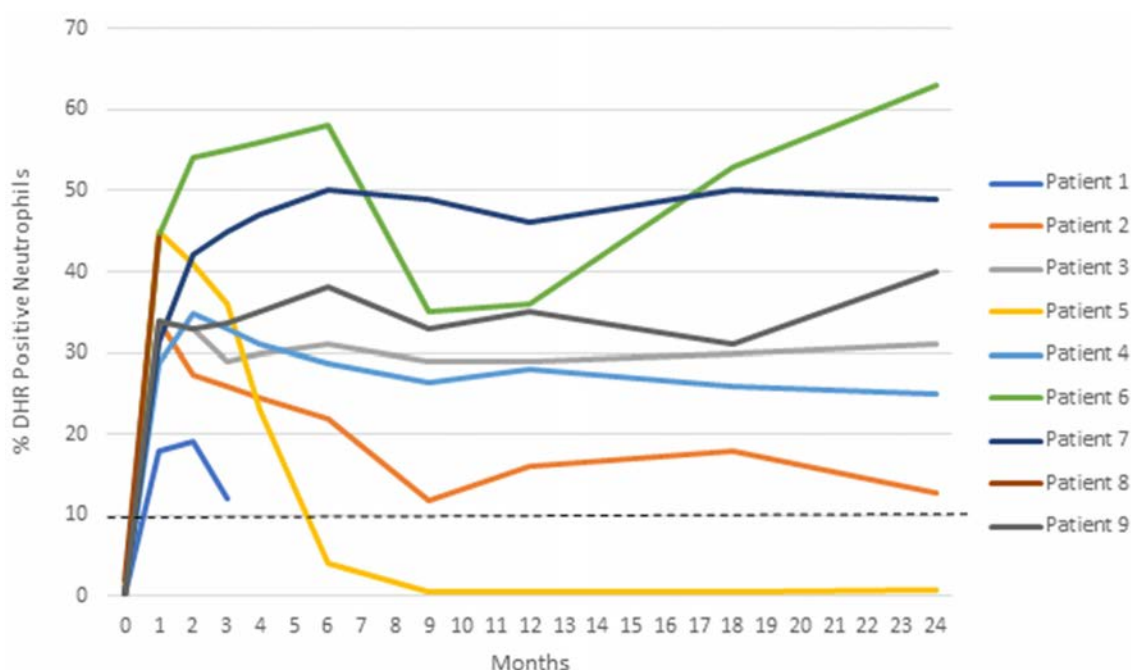
Ongoing clinical trials

OTL-102 is currently being investigated in two ongoing investigator-sponsored proof of concept clinical trials in the United States and in Europe, with target enrollment of 10 patients in a clinical trial sponsored by UCLA in the United States and target enrollment of five patients in a clinical trial conducted by GOSH in Europe. The clinical trial sites include Boston Children's Hospital, the NIH, and UCLA in the United States, and GOSH and The Royal Free Hospital in London. Manufacture of the drug product occurred at each of these sites using the same vector. As of July 2019, nine patients have been treated in the clinical trial in the United States, five of which were treated with a fresh product formulation and four of which were treated with a cryopreserved formulation. Further, three patients have been treated in the clinical trial in Europe, one of which was treated with a fresh product formulation and two of which were treated with a cryopreserved product formulation. One patient has been treated in a compassionate use program in Europe with a cryopreserved product formulation. In the future, we expect to treat additional patients in this trial with a cryopreserved formulation of OTL-102. Patients enrolled in these trials have advanced and severe stages of X-CGD.

The primary goals of these clinical trials are to assess safety and efficacy, as measured by biochemical and functional reconstitution through increased nicotinamide adenine dinucleotide phosphate-oxidase, or NADPH oxidase, activity in progeny of engrafted cells and stability at 12 months post-treatment.

In these clinical trials, the production of NADPH-oxidase activity in neutrophils, a biomarker that demonstrates restored granulocyte function, has been measured in patients for up to 24 months post-treatment. In a recent publication in *Nature Medicine*, combined data from nine patients, including initial enrollees in both clinical trials and a compassionate use patient, showed NADPH-oxidase activity, as measured by dihydrorhodamine, or DHR, assay, above 10% in six patients with at least 24 months follow-up. Based on the investigator’s review of the scientific literature, they determined that 10% was a clinically meaningful percentage for fighting infections successfully. One pediatric patient showed initial engraftment of DHR+ cells followed by a decrease to levels of 1% or less. The graphic below illustrates sustained NADPH-oxidase levels, as measured for up to 24 months post-treatment. Since September 2018, four additional patients have been treated as part of the clinical trials, with one adult patient having sustained DHR+ neutrophils of 77.2% at 6 months and three pediatric patients displaying a similar response to the pediatric patient that did not respond to therapy. These observations specific to the pediatric patients are under investigation, and investigators are planning to enroll additional pediatric patients in 2020 to assess outcomes in this patient population.

OTL-102 (X-CGD): oxidase activity⁽¹⁾



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

As of December 2019, the date of the most recent safety data available to us, safety data from the U.S. patients treated in this clinical trial indicate OTL-102 was generally well-tolerated, with no instances of insertional mutagenesis up to forty-eight months post-treatment. There were eighteen SAEs reported, none of which were assessed by the investigator as being possibly related to drug product. There were no AEs or SAEs leading to the withdrawal of patients from the trial. All AEs and SAEs resolved with standard of care treatment.

Because follow-up in this clinical trial is ongoing, safety data are preliminary and subject to change. As of the date of this Annual Report, we have not been notified by the investigator in this clinical trial of any SUSAR. In the U.K. study, eight SAEs were reported, one of which was deemed as possibly related to the product. The patient that suffered from this SAE experienced immune reconstitution inflammatory syndrome at initial engraftment of functional neutrophils, manifesting as pericardial effusion and abdominal pain, which resolved with steroid cover. This event is still under investigation by the data safety monitoring board.

Two patients treated with OTL-102 as part of the clinical trials died during the three months period following treatment as a result of pre-existing disease-related complications present at the time of treatment with OTL-102. One of these patients (from the U.K. trial) died of acute respiratory distress syndrome. This subject had a pre-existing lung condition. The other patient (from the U.S. trial) developed platelet antibodies due to sensitization after several granulocytes infusions the patient received prior to gene therapy. As a result, following gene therapy he was unable to respond to platelet transfusion and died from hemorrhage. Following this event, in September 2017, the investigators put this trial on hold, and after discussions with the FDA and the data safety monitoring board, the trial was re-initiated in February 2018. The learnings from this patient resulted in a protocol amendment to prevent patients with existing platelet antibodies from enrolling in the trial. Neither of these two fatalities was deemed by the investigator to be related to the therapy. A third fatality was reported involving a patient treated under the compassionate use program at GOSH. Because of this patient's advanced disease stage at the time of enrollment, the patient required a surgical procedure following treatment and died as a result of complications from this procedure. This fatality was deemed by the investigator not to be related to the product. It should be noted that this patient's data have been excluded from the data set in the clinical trials because the patient was treated with drug product manufactured under a different manufacturing process than that used for OTL-102, which was deemed by the investigator to be a different drug product than OTL-102.

Gene therapy for treatment of TDT

Disease overview

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

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

Limitations of current therapies

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

Our solution, OTL-300 for treatment of TDT

We are developing OTL-300 as an *ex vivo* lentiviral vector-mediated autologous HSC gene therapy to treat patients with TDT through a single administration. OTL-300 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood, then modified to add a functional HBB gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intra-osseous administration following treatment with a myeloablative conditioning regimen. We plan to investigate treatment through an intravenous administration of OTL-300 as part of the clinical development of this product candidate. OTL-300 is designed to significantly reduce or eliminate the need for blood transfusions in patients with TDT.

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

Proof of concept trial (cryopreserved formulation)

OTL-300 has been investigated in an academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The study and clinical follow-up completed in November 2019, and reporting is underway. Nine patients with severe TDT received a single intra-osseous infusion of a cryopreserved formulation of OTL-300 and were followed up for 2 years. The patients evaluated in this trial included six pediatric patients aged three to 17 years, and three

adult patients aged 18 years and over. On completion of the study, all patients enrolled in an Orchard-sponsored long-term follow-up clinical trial, which will continue assessment for an additional six-year period.

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

As of November 2019, all patients had completed at least 21 months of post-treatment follow-up. Transfusion independence or significant reductions in transfusion frequency and volume requirements were observed in six patients, with four of the six pediatric patients being transfusion-free since approximately one-month post-treatment (follow-up ranging from 21-39 months). Following treatment, substantial reductions (in excess of 50%) in transfusion volume requirements were observed over a period of at least 3 years in two out of three adult patients, one of whom had a 9-month transfusion-free period during the first-year post-treatment.

As of April 2019, the date of the most recent development safety update report, 100% overall survival has been observed, with follow-up ranging from 16 to 43 months. Safety data from the nine patients treated to date indicate that OTL-300 was generally well-tolerated, with no instances of insertional mutagenesis. There were five SAEs reported, none of which were assessed by the investigator as being related to OTL-300. The SAEs included central line and mycobacterium infection, febrile neutropenia, gastroenteritis, and obstructive pancreatitis due to gall stones. There were no AEs or SAEs leading to the withdrawal of patients from the trial. All SAEs resolved with standard of care treatment. Because follow-up in this clinical trial is ongoing, safety data are preliminary and subject to change. As of the date of this Annual Report, we have not been notified by the investigator in this clinical trial of any SUSAR.

Gene therapy for treatment of MPS-I

Disease overview

Mucopolysaccharidosis type I is a lysosomal storage disease caused by a deficiency of the lysosomal enzyme alpha-L-iduronidase, or IDUA. Inherited deficiency of IDUA is responsible for MPS-I. The disease is characterized by inappropriate storage of glycosaminoglycans, or GAGs, with accompanying organ enlargement, the excretion of abnormal quantities of GAGs in urine, and disrupted GAG turnover that especially affects connective tissues and the nervous system. Without treatment, clinical manifestations of this severe disease include skeletal abnormalities with severe orthopedic manifestations, hepatosplenomegaly, neurodevelopmental decline, sight and hearing disturbances, cardiovascular and respiratory problems leading to death in early childhood. IDUA deficiency can result in a wide range of clinical severity, with 3 major recognized clinical entities: Hurler, or MPS IH, Scheie, or MPS IS, and Hurler-Scheie, or MPS IH/S, syndromes. Hurler and Scheie syndromes represent phenotypes at the severe and attenuated ends of the MPS-I clinical spectrum, respectively, and the Hurler-Scheie syndrome is intermediate in phenotypic expression.

MPS IH is usually associated to the presence of two nonsense mutations resulting in the complete absence of residual enzyme activity. MPS IH is characterized by a chronic, progressive and disabling disease course involving multiple organs and tissues. The median age of diagnosis for MPS IH is 12 months; most affected children are diagnosed before 18 months of age. Infants affected by MPS IH usually appear normal at birth, but may develop inguinal or umbilical hernias in the first six months, and develop the characteristic somatic phenotype over the first few years of life.

The approximate incidence of MPS-I is of 1 in 100,000 live births.

Limitations of current therapies

Because of its potential to compensate the deficiency, ERT – parenteral administration of purified recombinant pro-enzyme – has become the most promising therapeutic option for some LSDs, including for some forms of MPS-I. However, systemic administration of ERT only partially addresses the systemic manifestations of the disease, particularly orthopedic and skeletal symptoms. In addition, the blood-brain barrier severely limits access of systemically administered therapeutic molecules to the nervous tissue, greatly reducing the therapeutic impact of this strategy. Thus, ERT is not currently recommended as a unique treatment option for MPS IH patients, except for the preparatory phases of allogeneic transplantation.

HSCT has been provided to more than 500 MPS IH patients with the goal of providing a stable endogenous source of functional IDUA enzyme. Although HSCT has been shown to be clinically effective, increasing life expectancy and

improving various clinical outcomes, the impact of HSCT on the central nervous system, or CNS, and skeletal disease has been shown to be suboptimal, likely due to insufficient metabolic correction by the IDUA enzyme at these disease sites.

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

Ex vivo lentiviral vector mediated autologous HSC gene therapy strategies aimed at correcting the genetic defect in patients' HSCs could represent a significant improvement for the treatment of MPS IH when compared to conventional allogeneic HSCT. Autologous cells may be genetically modified to constitutively express supra-normal levels of the therapeutic enzyme and become a quantitatively more effective source of functional enzyme than wild-type cells, possibly also at the level of the nervous system and bone. The therapeutic potential of this strategy for addressing the extensive nervous system manifestations of MPS IH is based on the contribution of HSCs to the turnover of CNS-resident microglia, demonstrated both in physiological and pathological conditions. Since microglia have been implicated in the pathogenesis of a number of neurodegenerative conditions, including LSDs, these cells should be considered a primary target cell type in therapeutic strategies for LSD with neurologic involvement such as MPS IH. Moreover, compared to allogeneic transplantation, the autologous procedure is associated to a significantly reduced transplant-related morbidity and mortality and avoids the risks of graft versus host disease.

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, monocentric, therapeutic-exploratory, single dose, proof of concept, non-randomized, open label study involving a single injection of autologous HSCs genetically modified with a lentiviral vector. The target enrollment in this trial is eight patients with a confirmed diagnosis of MPS IH, and all eight patients have now been enrolled and received a single dose of a cryopreserved formulation of OTL-203. The patients evaluated in this trial include pediatric patients aged ≥ 28 days and ≤ 11 years old and will be followed for at least 2 years post-treatment in the context of the proof of concept study and then continue to be evaluated in a long-term follow-up study.

The primary endpoints of the trial are safety, haematological engraftment by day 45 following treatment and preliminary efficacy as measured by IDUA enzyme activity (up to supraphysiologic levels) at one-year post-treatment.

Preliminary data from the proof of concept study with OTL-203 has demonstrated:

- OTL-203, the mobilising protocol and the selected conditioning regime were well-tolerated
- Rapid hematologic reconstitution, with neutrophil and platelet engraftment within three weeks following treatment
- Engraftment in the bone marrow and periphery by assessment of the vector copy number
- Supranormal IDUA enzyme expression in peripheral blood

Key secondary and exploratory endpoints include normalization of urinary GAGs, growth velocity and effects on motor and cognitive function at one- and two-years post-treatment.

For the first six treated patients, with up to 12 months of follow-up in one patient and a median follow-up of 6 months, restoration of IDUA enzyme activity in the periphery to supranormal levels and reduction of GAG levels in the urine was observed. Furthermore, restoration of IDUA activity in cerebrospinal fluid, or CSF, and reduction of GAG levels in CSF was observed in four patients, with up to 12 months of follow-up in one patient and a median follow-up of 6 months.

For the patient with 12 months of follow-up, preliminary clinical evaluation showed signs of resumed growth, improved motor skills and a stable cognitive score.

We expect to release interim data for this trial in 2020, with 12-month follow-up results for the first eight patients, including the primary endpoints, anticipated in 2021.

OTL-203 has received orphan drug designation from the EMA for the treatment of MPS-I.

Our gene therapy programs for the treatment of MPS-IIIA and MPS-IIIB

Disease overview

MPS-III A (also known as Sanfilippo syndrome type A) and MPS-III B (also known as Sanfilippo syndrome type B) are life-threatening metabolic diseases that cause accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within one to two years after birth, MPS-III A and MPS-III B patients begin to experience progressive neurodevelopmental decline, including speech delay and eventual loss of language, behavioral disturbances, and potentially severe dementia. Ultimately, most patients with MPS-III A progress to a vegetative state. Life expectancy for patients with MPS-III A and MPS-III B is between 10 to 25 years and 15 to 30 years, respectively.

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

Limitations of current therapies

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

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

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

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

Proof of concept trial in MPS-III A

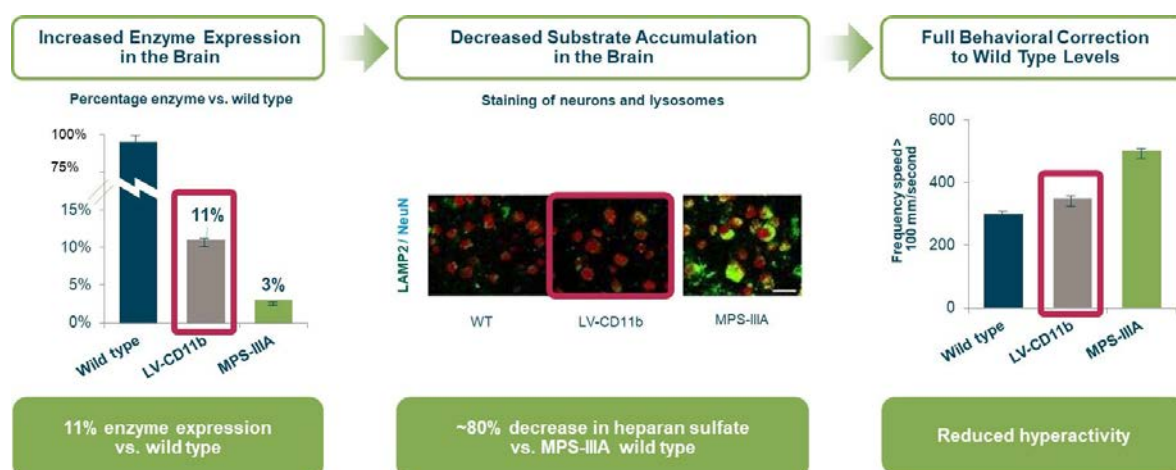
We are supporting a proof of concept trial for the treatment of MPS-III A, which started enrollment in January 2020. The trial is expected to enroll up to five patients in 2020 and is being conducted by the Royal Manchester Children's Hospital and sponsored by the Manchester University NHS Foundation Trust. In early 2019, a child with MPS-III A was treated by Royal Manchester Children's Hospital outside of the clinical trial, though utilizing the same technology and procedures, under a "Specials" license granted by the UK government for the use of an unlicensed pharmaceutical product in situations of high unmet need when there is no other treatment option available.

Preclinical development of MPS-III B

In a mouse model of MPS-III A, engraftment of donor HSCs modified with the selected vector for this program (a hCD11b-coSGSH lentiviral vector) was observed. Sustained gene expression of the gene-modified HSCs was seen over a follow-up period of approximately six months, which we believe supports the stability of the engraftment of modified cells.

Transplantation of gene-modified HSCs resulted in a 4.72-fold increase in enzyme activity relative to wild type enzyme levels and significantly elevated brain enzyme activity. Increased enzyme activity resulted in decreased heparan sulphate substrate accumulation in the brain and correction of behavioral abnormalities, such as hyperactivity and a reduced sense of danger, to normal levels.

The figures below illustrate the increased enzyme expression observed in the brain, the corresponding decreased substrate accumulation in the brain, and the resulting behavioral correction in a mouse model of MPS-III A.



Preclinical studies in a mouse model of MPS-III B have demonstrated correction of neurological activity, as measured by reduction in hyperactivity. Lentivirus vector optimization for OTL-202 for treatment of MPS-III B is ongoing, and we plan to continue to progress preclinical development of MPS-III B.

Preclinical data for our gene therapy programs

Each of our aforementioned lead programs has been evaluated in preclinical studies of murine models of the target indications. Preclinical development plans have been discussed with or reviewed by the FDA and EMA or European Union Member State Authorities over the course of drug development interactions or approval of clinical trials.

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 rare diseases. Although our initial focus is on delivering our commercial and clinical-stage gene therapies to patients suffering from ADA-SCID, MLD, WAS, X-CGD, MPS-I, MPS-III A, and TDT, we believe we can leverage our significant research and development experience and partnerships with academic institutions to identify other diseases in our target franchise areas, including primary immune deficiencies, neurometabolic disorders and blood disorders, where *ex vivo* gene therapy has a comparably high probability of success.

Our regulatory strategy

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare or ultra-rare indications, we believe our clinical programs will generally be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. Both the FDA and the EMA provide expedited pathways for the development of drug product candidates for the treatment of rare diseases, particularly life-threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following one or more clinical trials in a limited patient population, following review of the trial's design, endpoints and clinical data by the applicable regulatory agencies. These determinations are based on the applicable regulatory agency's scientific judgement and these determinations may differ in the United States and the European Union.

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

fresh drug product. For purposes of this Annual Report we refer to these clinical trials as supportive clinical trials. In addition, certain of our product candidates may be evaluated in clinical trials for which clinical data is not intended to be pooled with data from our registrational trials for purposes of a regulatory submission, but will be submitted to the applicable regulatory agencies for informational purposes. For purposes of this Annual Report we refer to these trials as additional clinical trials. In addition, in some cases patients may be ineligible for participation in our clinical trials and may receive treatment under a compassionate use program or an expanded access program. We expect that the available safety and efficacy results from all these trials would be included in any regulatory submission we may submit and the applicable regulatory agency with respect to each clinical program the applicable regulatory agency will make a determination as to whether the available data is sufficient to support a regulatory submission. See *Item 1A. Risk Factors*—“The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission or granting of marketing approval for our product candidates,” “We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product,” and “To date, most of the clinical trials for our product candidates were conducted as investigator sponsored clinical trials using drug product manufactured at the academic sites.”

Manufacturing

The diseases we are targeting affect patients across the world. Therefore, we are implementing our plans to build a commercial-scale manufacturing infrastructure 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 Oxford BioMedica and MolMed S.p.A., for the supply of our vectors and/or drug product. We have established relationships with commercial CDMO partners with the resources and capacity to meet our clinical and existing and expected initial commercial needs. Two of our vector CDMOs currently manufacture for approved commercial gene therapy products. Our CDMO partners also provide us with access to their state-of-the-art manufacturing technologies.

Manufacturing efficiencies and scalability

We are investing in infrastructure, technologies and human capital to build manufacturing capabilities for HSC based autologous *ex vivo* gene therapy. We currently operate one process development laboratory facility in Menlo Park, California. We are in the process of building an integrated facility in Fremont, California designed to accommodate our needs to grow our process development capabilities and establish in-house manufacturing to ensure reliable supply of vector and drug products for clinical and commercial use. We have on-going effort 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 the processes with an ultimate goal to produce high quality products for global rare disease patients at lower cost. We continue to invest in our people to support the commercialization and lifecycle management of our pipeline products. We believe our strategy could enable the industrialization of the scientific breakthroughs in gene therapy research to bring potential cures to the rare disease patients worldwide.

Cryopreservation of our gene therapy programs

Cryopreservation of the gene-modified cells is a key component of our strategy to deliver potentially transformative gene therapies to patients worldwide. We have developed cryopreserved formulations of our OTL-101, OTL-102, OTL-103, programs and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future submissions for marketing approval in the United States and Europe. Our programs in OTL-102, OTL-300, OTL-203 and OTL-201 have already started or will start with cryopreserved formulations. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

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

Commercial operations

Subject to approval from the EMA of OTL-200 for the treatment of MLD, which is anticipated in the second half of 2020, we expect to launch OTL-200 in Europe. As we plan to support the potential launch of OTL-200, we have started to build commercial operations in Europe and the United States with a goal of delivering OTL-200 to patients through qualified treatment centers. We have begun a phased build of commercial capabilities by adding employees with broad experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement. We expect to continue expansion of these capabilities throughout 2020 and beyond as we continue to implement appropriate quality systems, compliance policies, systems and procedures, as well as internal systems and infrastructure in order to support our complex supply chain, qualify and train 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. Ultimately, we intend to utilize the commercial infrastructure that we build to support the potential for multiple product launches, if approved, sequentially across multiple geographies. For many territories and countries, we may also elect to utilize strategic partners, distributors, or contract field-based teams to assist in the commercialization of our products.

Intellectual property and barriers to entry

Our commercial success depends, in part, upon our ability to protect commercially important and proprietary aspects of our business, defend and enforce our intellectual property rights, preserve the confidentiality of our know-how and trade secrets, and operate without infringing misappropriating and otherwise violating valid and enforceable intellectual property rights of others. In particular, we strive to protect the proprietary aspects of our business and to develop barriers to entry that we believe are important to the development and commercialization of our gene therapies. For example, where appropriate, we develop, or acquire exclusive rights to, clinical data for each of our products/product candidates, patents, know-how and trade secrets associated with each of our products/product candidates. However, we do not own any patents or patent applications that cover Strimvelis or any of our lead product candidates. We in-license from UCLB and UCLA one family of patent applications directed at OTL-101. We cannot guarantee that patents will issue from any of these patent applications or from any patent applications we or our licensors may file in the future, nor can we guarantee that any patents that may issue in the future from such patent applications will be commercially useful in protecting our products/product candidates. In addition, we plan to rely on regulatory protection based on orphan drug exclusivities, data exclusivities and market exclusivities. See “—Government regulation” for additional information.

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

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

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

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

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

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

License agreements

GSK asset purchase and license agreement

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

Under the GSK Agreement, we are subject to certain obligations to develop and advance certain of the acquired product candidates. For example, we are required to first use best endeavors to file an MAA for OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. We are also required to use best endeavors to file a BLA for OTL-103 for WAS in the United States and to use commercially reasonable efforts to file an MAA for OTL-103 in Europe, and to subsequently market, sell and promote OTL-103 in such jurisdictions. We are also required to use commercially reasonable efforts to develop and file an MAA or BLA, as applicable, for OTL-300 for TDT in either the United States or Europe. In addition, we must also use best endeavors to maintain the MAA and regulatory designations for Strimvelis in the European Union and to continue to make Strimvelis available to eligible patients until an alternative gene therapy product has received marketing approval in Europe. We must also continue to make Strimvelis available at the San Raffaele Hospital for as long as a minimum number of patients are treated and entitled to receive reimbursement for the provision of Strimvelis, over a defined period. We intend to continue to make Strimvelis available for so long as we are required to do so under the GSK Agreement.

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

GSK received a one-time upfront fee of £10.0 million under the GSK Agreement, and we issued to GSK 12,455,252 of our Series B-2 convertible preferred shares and we recorded a payable due to GSK of £4.9 million, of which £2.5 million is outstanding as of December 31, 2019. The Series B-2 convertible preferred shares were converted to ordinary shares as part of our initial public offering.

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. We will pay a mid-single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048.

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

Telethon-OSR research and development collaboration and license agreement

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

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicensable license under certain intellectual property rights to develop and commercialize *ex vivo* gene therapy products for the treatment of ADA-SCID. In addition, Telethon-OSR had granted to GSK an exclusive option for an exclusive, sublicensable, worldwide license under certain intellectual property rights to develop and commercialize certain vectors and gene therapy products from disease-specific development programs for the treatment of WAS, MLD, TDT, as well as three additional earlier-stage development programs. Our options under the R&D Agreement with respect to the three earlier-stage programs have lapsed. At the time we entered into the deed of novation agreement, GSK had completed development, launched and commercialized Strimvelis for ADA-SCID in the European Union, and had exercised its exclusive option to obtain exclusive licenses from Telethon-OSR to the WAS, MLD and TDT programs. We acquired Strimvelis and GSK's exclusive licenses relating to the ADA-SCID, WAS, MLD and TDT collaboration programs pursuant to the GSK Agreement and to the deed of novation.

Under the R&D Agreement, Telethon-OSR is required to use commercially reasonable efforts to conduct each of the collaboration programs in accordance with development plans approved by a joint steering committee. With respect to those programs in relation to which our option has been exercised, we are required to use commercially reasonable efforts to develop, obtain regulatory approval, launch and promote in both the European Union and the United States all licensed products and to commercialize and manufacture such products at levels sufficient to meet commercial demands. We are required to use best efforts to renew the European Union marketing authorization for Strimvelis to enable patients to be treated at the San Raffaele hospital from all referring centers globally, as permitted by applicable law. With certain exceptions, Telethon-OSR is responsible for all costs and activities associated with the collaboration programs prior to our exercise of the option for any such program. 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 also required to pay Telethon-OSR a fee in connection with the exercise of our option for each collaboration program. We are obligated to pay up to an aggregate of €31.0 million in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDT programs). Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves a certain threshold percentage of the market share.

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

UCLB/UCLA license agreement

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

UCLB received an aggregate upfront fee of £1.4 million and a patent reimbursement fee of £12,524 under the UCLB/UCLA Agreement, and we issued to UCLB 1,224,094, and 3,441,290 of our ordinary shares in 2017 and 2016, respectively. We are also required to make certain annual administration payments to UCLB upon our receipt of VAT invoices.

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

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

Oxford BioMedica license and development agreement

In November 2016, we entered into a license and development agreement, or the Oxford Development Agreement, with Oxford BioMedica (UK) Limited, or Oxford BioMedica, for the development of gene therapies for ADA-SCID, MPS-III A and certain other diseases that we may request be included under the Oxford Development Agreement, such other diseases referred to as Subsequent Indications. The Oxford Development Agreement was amended in June 2017, May 2018, July 2018 and September 2018.

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

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

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

Telethon-OSR license agreement

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

Competition

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

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

We are currently aware of the following competitive approaches:

- **ADA-SCID:** The current standards of care for the treatment of ADA-SCID are HSCT and chronic ERT. In October 2018, the FDA approved elapegamase-lvlr (tradename Revcovi), a PEGylated recombinant ADA ERT marketed by Leadiant Biosciences to treat ADA-SCID.
- **MLD:** To our knowledge, there is currently no effective treatment option for patients with MLD. HSCT has demonstrated limited efficacy in arresting disease progression and is therefore not considered a standard of care for this disease. A number of alternative approaches to HSCT are under investigation. We are aware that the Institut National de la Santé Et de la Recherche Médicale and Bicêtre hospital in Paris are investigating intracerebral gene therapy for MLD. We are also aware that Takeda is investigating ERT for MLD with a biweekly intrathecal infusion. We are also aware that Shenzhen University is evaluating a lentiviral *ex vivo* gene therapy for MLD.
- **WAS:** The current standard of care for WAS is HSCT. Patients who are unable to match with a blood donor or who are otherwise ineligible for HSCT may pursue palliative care options, including intravenous immunoglobulin and antimicrobials to prevent and treat infections, topical corticosteroids to manage outbreaks of eczema, platelet transfusions to treat severe bleeds, and immunosuppressive drugs, such as rituximab (tradename Rituxan), to counter autoimmune manifestations. Splenectomy may also be used to treat thrombocytopenia. These palliative approaches do not slow disease progression or address the underlying cause of WAS. We are also aware that Généthon and Boston Children's Hospital are sponsoring clinical trials with *ex vivo* autologous lentiviral gene therapy.
- **X-CGD:** Management options for patients with X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma therapy. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. We are aware that Généthon is sponsoring a clinical trial in France for X-CGD with an *ex vivo* autologous lentiviral gene therapy.
- **MPS-I:** The current standard of care for the treatment of MPS-I involves regular intravenous injections of laronidase (tradename Aldurazyme), an ERT commercialized by BioMarin and Sanofi Genzyme. A formulation of laronidase for intrathecal administration is currently under evaluation. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. We are aware that RegenX Bio is developing RGX-111, an AAV-based gene therapy, and that ArmaGen is developing AGT-181, an ERT. Additionally, Sangamo Therapeutics has a program using zinc-finger nucleases to insert a functional copy the IDUA gene into liver cells, and Magenta Therapeutics is conducting clinical trials to evaluate MGTA-456, an agent to expand cord-blood for use in HSCT to treat MPS-I.

- **MPS-III A:** There are currently no effective disease modifying treatment options for patients with MPS-III A. We are aware of three gene therapy candidates in clinical development. Lysogene is developing SAF-302 in collaboration with Sarepta Therapeutics, an AAV10 gene therapy product administered through intracerebral injections, Abeona Therapeutics is developing ABO-120, an AAV9 gene therapy product administered intravenously, and Esteve is developing EGT-101, an AAV9 gene therapy administered through intracerebroventricular injection. Currently no companies are developing ERTs for MPS-III A.
- **TDT:** The current standard of care for the treatment of TDT involves chronic blood transfusions to address anemia combined with iron chelation therapy to manage the iron overload often associated with such chronic blood transfusions. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. TDT is a highly competitive research area with one approved treatment option and several novel approaches under investigation. In June 2019 the EMA approved LentiGlobin (under the trade name Zynteglo) an *ex vivo* autologous gene therapy marketed by bluebird bio for the treatment of patients aged 12 years and over with less severe (non- β^0/β^0 genotype) TDT and without an HLA-matched donor. bluebird bio has publicly announced its intention to file a BLA in the United States for LentiGlobin in 2020, as well as label expansions in other TDT genotypes. In addition, CRISPR Therapeutics and Vertex are conducting a study of gene editing cell therapy in patients with TDT, and Sangamo is also conducting a study with a gene editing approach to treat TDT. Luspatercept-aamt (tradename Reblozyl), which is being jointly developed by Bristol-Myers Squibb and Acceleron Pharma, was approved in the United States in November 2019 for the treatment of anemia in adult patients with beta-thalassemia who require regular red blood cell transfusions. Several other non-gene therapy approaches are under investigation to improve treatment outcomes in beta-thalassemia.

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

Government regulation

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

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

U.S. biological products development process

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

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

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

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

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

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

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

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

In addition to the submission of an IND to the FDA before initiation of a clinical trial in the United States, certain human clinical trials involving recombinant or synthetic nucleic acid molecules had historically been subject to review by the Recombinant DNA Advisory Committee, or RAC, of the NIH, Office of Biotechnology Activities, or the OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. While the NIH Guidelines are not mandatory unless the research in question being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. On August 17, 2018, the NIH issued a notice in the Federal Register and issued a public statement proposing changes to the oversight framework for gene therapy trials, including changes to the applicable NIH Guidelines to modify the roles and responsibilities of the RAC with respect to human clinical trials of gene therapy products, and requesting public comment on its proposed modifications. During the public comment period, which closed October 16, 2018, the NIH announced that it will no longer accept new human gene transfer protocols for review as a part of the protocol registration process or convene the RAC to review individual clinical protocols. In April 2019, NIH announced the updated guidelines, which reflect these proposed changes, and clarified that these trials will remain subject to the FDA's oversight and other clinical trial regulations, and oversight at the local level will continue as set forth in the NIH Guidelines. Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. Further, NIH renamed the RAC the Novel and Exceptional Technology and Research Advisory Committee, or NExTRAC, and revised its role to provide recommendations to the NIH Director and a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies.

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

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

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

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

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

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

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

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

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

U.S. review and approval processes

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

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

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

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the CGTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through appropriate screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. 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.

Expedited development and review programs

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

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

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

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

RMAT designation

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

Post-approval requirements

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

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

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

U.S. patent term restoration and marketing exclusivity

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

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

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

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

Additional regulation

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

U.S. Foreign Corrupt Practices Act

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

Government regulation outside of the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products as well as authorization and approval of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted for each clinical trial to each country's national health authority and an independent ethics committee, much like the FDA and an IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical trial may proceed.

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.

Regulation in the European Union

In the European Union, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the European Union and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products, which are cells or tissues that have undergone substantial manipulation and that are administered to human beings in order to regenerate, repair or replace a human tissue. We anticipate that our gene therapy development products would be regulated as ATMPs in the European Union.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit an MAA. The application used to submit the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application during the eight year period. 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. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may therefore not qualify for data exclusivity. Products with an orphan designation in the European Union can receive ten years of market exclusivity, during which time "no similar medicinal product" for the same indication may be placed on the market. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. An orphan product can also obtain an additional two years of market exclusivity in the European Union 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 European Union 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 is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the European Union when the application is made; or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

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

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, 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.

Pediatric development

In the European Union, companies developing a new medicinal product must agree upon a Pediatric Investigation Plan, or PIP, with the EMA, 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 marketing authorization application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Post-approval controls

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved SmPC and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the European Union. Although general requirements for advertising and promotion of medicinal products are established under European Union directives, the details are governed by regulations in each European Union Member State and can differ from one country to another.

Brexit and the Regulatory Framework in the United Kingdom

In June 2016, the electorate in the United Kingdom voted in favor of leaving the European Union (commonly referred to as “Brexit”). Thereafter, in March 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The United Kingdom formally left the European Union on January 31, 2020. A transition period began on February 1, 2020, during which European Union pharmaceutical law remains applicable to the United Kingdom. This transition period is due to end on December 31, 2020. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

Other healthcare laws and compliance requirements

In the United States, our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs may have to comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy and security provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended, as applicable:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;
- the federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payers if they are deemed to “cause” the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary’s selection of a particular supplier of items or services reimbursable by a federal or state governmental program;

- HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payer (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

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

We may also be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, or EEA, including personal health data, is subject to the General Data Protection Regulation 2016/679 (GDPR), which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR includes restrictions on cross-border data transfers. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities.

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

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

Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive stock 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, any of which could adversely affect our ability to operate our business and our financial results. In addition, our gene therapy program, Strimvelis, was approved by the EMA in 2016, and the approval and commercialization of Strimvelis subjects us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws. The approval and commercialization of any of our other gene therapies outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

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

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

Healthcare reform

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

Some of the provisions of the ACA have yet to be implemented, and there have been legal and political challenges to certain aspects of the ACA. Since January 2017, President Trump has signed two executive orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the ACA. On January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. The Trump administration has concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until those appropriations are made. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the cost share reduction payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payors who argued the payments were owed to them. This was appealed to the U.S. Supreme Court, which heard arguments on December 10, 2019.

Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the “individual mandate.” On December 14, 2018, a federal district court in Texas ruled the individual mandate is a critical and inseparable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional, and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. In December 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program in response to the outcome of the federal district court litigation regarding the method CMS uses to determine this risk adjustment. In addition, CMS published a final rule that would give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

On January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA -mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices; however, on December 20, 2019, President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. The Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole”.

Other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction of at least \$1.2 trillion for fiscal years 2012 through 2021, triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect beginning on April 1, 2013 and, due to legislation amendments to the statute, including the BBA, will stay in effect through 2029 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 and 2020 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. While a number of these and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on September 25, 2019, the Senate Finance Committee introduced the Prescription Drug Pricing Reduction Action of 2019, a bill intended to reduce Medicare and Medicaid prescription drug prices. The proposed legislation would restructure the Part D benefit, modify payment methodologies for certain drugs, and impose an inflation cap on drug price increases. An even more restrictive bill, the Lower Drug Costs Now Act of 2019, was introduced in the House of Representatives on September 19, 2019, and would require the Department of Health and Human Services (HHS) to directly negotiate drug prices with manufacturers. The Lower Drugs Costs Now Act of 2019 has passed out of the House and was delivered to the Senate on December 16, 2019. However, it is unclear whether either of these bills will make it through both chambers and be signed into law, and if either is enacted, what effect it would have on our business. Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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

Coverage and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any gene therapies for which we obtain regulatory approval. In the United States and markets in other countries, sales of any gene therapies for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and reimbursement from payors. Payors include government authorities, managed care providers, private health insurers and other organizations. Patients who are prescribed treatments for their conditions and providers generally rely on these third-party payors to reimburse all or part of the associated healthcare. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payer 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.

In addition, coverage and reimbursement for products can differ significantly from payer to payer. 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 payer 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 clinical trials in order to demonstrate the medical necessity and cost-effectiveness of such product, in addition to the costs required to obtain regulatory approvals. If payors do not consider a product to be cost-effective compared to other available therapies, 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 sell its products at a profit.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, in the European Union, 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. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures.

Employees

As of December 31, 2019, we had 252 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 good.

Corporate Information

We were originally incorporated under the laws of England and Wales in August 2018 as Orchard Rx Limited (now known as Orchard Therapeutics plc) to become a holding company for Orchard Therapeutics (Europe) Limited (previously known as Orchard Therapeutics Limited). Orchard Rx Limited subsequently re-registered as a public limited company and its name was changed from Orchard Rx Limited to Orchard Therapeutics plc in October 2018. Orchard Therapeutics (Europe) Limited was originally incorporated under the laws of England and Wales in September 2015 as Newincco 1387 Limited and subsequently changed its name to Orchard Therapeutics Limited in November 2015 and to Orchard Therapeutics (Europe) Limited in October 2018. Our registered office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom, and our telephone number is +44 (0) 203 808 8286. Our website address is www.orchard-tx.com. We do not incorporate the information on or accessible through our website into this Annual Report, and you should not consider any information on, or that can be accessed through, our website as part of this Annual Report. We make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file or furnish such materials to the U.S. Securities and Exchange Commission.

Item 1A. Risk Factors.

Our business faces significant risks. This section of the Annual Report highlights some of the risks that may affect our future operating results. You should carefully consider the risks described below, as well as in our consolidated financial statements and the related notes included elsewhere in this Annual Report and in our other SEC filings. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and/or growth prospects. This Annual Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in these 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 \$163.4 million, \$230.5 million, and \$39.7 million for the years ended December 31, 2019, 2018, and 2017, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares and through sales of our ADSs in our initial public offering and follow-on offering. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union, building a global commercial infrastructure to support anticipated commercialization of our product candidates, including OTL-101 for adenosine deaminase-severe combined immunodeficiency, or ADA-SCID, OTL-200 for metachromatic leukodystrophy, or MLD, and OTL-103 for Wiskott-Aldrich syndrome, or WAS, if such product candidates are approved, as well as expanding our team. To date, Strimvelis is our only commercialized product, and absent the realization of sufficient revenues from product sales of Strimvelis or our current or future product candidates, if approved, we may never attain profitability. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if, and as, we:

- seek marketing approvals for our product candidates that successfully complete clinical trials or meet primary endpoints, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of Strimvelis in the European Union, and 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 of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and our ongoing and planned clinical trials of OTL-102 for X-CGD, OTL-203 for MPS-I, OTL-201 for MPS-IIIa and OTL-300 for transfusion-dependent beta-thalassemia, or TDT, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- conduct investigational new drug application, or IND- or clinical trial application, or CTA-, enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates;
- 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 and to support manufacturing of product to commercial scale;
- develop our own in-house manufacturing operations;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality, regulatory affairs, process development, manufacturing, supply chain, engineering, 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.

Strimvelis is our only product that has been approved for sale and, to date, it has only been approved in the European Union for the treatment of ADA-SCID. Since receiving marketing authorization, only a limited number of patients have been treated with Strimvelis. Our revenue from sales of Strimvelis alone will not be sufficient for us to become profitable. Under the terms of our asset purchase and license agreement with GSK, or the GSK Agreement, we are required to use our best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients, and at all times at the San Raffaele Hospital

in Milan, Italy, provided that a minimum number of patients continue to be treated at this site. 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 substantially as we seek to complete necessary preclinical studies and clinical trials of our product candidates, and manufacture, market and sell these or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

We have only generated revenue from sales of Strimvelis, 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 begun generating revenue from the sale of Strimvelis, we do not expect to achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. For example, in connection with our transaction with GSK in April 2018, we recorded a liability for Strimvelis representing the fair value of the future expected costs to maintain the marketing authorization in excess of expected future sales. Our ability to generate future revenues from product sales depends heavily on our and or our collaborators' success in:

- completing research and preclinical development of our product candidates and identifying new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing 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 regulatory compliance for Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for 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 Strimvelis and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and manufacturing capabilities;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

We anticipate incurring significant costs associated with commercializing any products for which we obtain marketing approval. Our expenses could increase beyond expectations if we are required by the United States Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate or if we encounter delays or clinical holds in the development of our product candidates. Even if we continue to generate revenue from sales of Strimvelis and are able to generate revenues from the sale of any other approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain 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 in 2019, primarily due to our net loss of \$163.4 million for that year. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the expansion of our commercial infrastructure in support of Strimvelis and our anticipated commercialization of OTL-101 for ADA-SCID, OTL-200 for MLD, and OTL-103 for WAS, if such product candidates are approved, continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and continue to enhance and optimize our vector technology and manufacturing processes, including building out our in-house drug product and vector manufacturing capabilities. 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 Strimvelis and any other products for which we obtain marketing approval. Furthermore, we will continue to incur additional 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, and our independent auditor's attestation report on our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. 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 research and development programs and/or commercialization efforts.

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

- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities required, including quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution, to support Strimvelis in the European Union and any other products for which we obtain marketing approval;
- qualifying for, and maintaining adequate coverage and reimbursement by, government and payors on a timely basis for Strimvelis 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 regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our product candidates;
- 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 Strimvelis and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;

- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

Identifying potential product candidates and conducting preclinical testing and clinical trials, as well as preparing for the potential commercialization of these product candidates, is a time-consuming, expensive and uncertain process that takes years to complete. We may never generate the necessary data or results required to obtain marketing approval and achieve product sales for any products other than Strimvelis. In addition, Strimvelis or any other products for which we obtain marketing approval may not achieve commercial success. Any product revenues from our product candidates, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

We may seek to raise capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise capital through the sale of equity, convertible debt securities or other equity-based derivative securities, ownership percentages of all our shareholders may be diluted and the terms may include liquidation or other preferences that adversely affect their rights as shareholders. Any indebtedness we incur would result in 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 and alliances and 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.

Our limited operating history may make it difficult to evaluate the success of our business to date and to assess our future viability.

We were incorporated in August 2018 to become a holding company for Orchard Therapeutics (Europe) Limited, which was founded in 2015, and its subsidiaries. Our operations, to date, have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring certain of our product candidate portfolios and rights to our technology, identifying potential product candidates, undertaking preclinical studies and planning and supporting clinical trials of our product candidates, establishing research and development and manufacturing capabilities, establishing a quality management system, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union and building a global commercial infrastructure to support anticipated commercialization of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if such product candidates are approved. We have not yet demonstrated the ability to obtain marketing approvals, manufacture products on a commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and setbacks.

Risks related to the discovery, development and regulatory approval of our product candidates

Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our autologous *ex vivo* gene therapy approach, and our future success depends on our successful development of commercially viable gene therapy products. There can be no assurance that we will not experience problems or delays in developing new products and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. Although we have established a commercial infrastructure for the production of Strimvelis in the European Union and we are building a global commercial infrastructure to support commercialization of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if such product candidates are approved, we may experience delays in establishing a sustainable, reproducible and scalable manufacturing capability in-house and at 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 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 or the European Union or other jurisdictions or how long it will take to commercialize 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.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. Such requirements may lengthen the regulatory review process, require us to perform additional studies, and increase our development costs or may force us to delay, limit, or terminate certain of our programs.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. The FDA has established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review when called upon. The NIH has refocused the NIH Recombinant DNA Advisory Committee and changed its name to the Novel and Exceptional Technology and Research Advisory Committee, or NEXTRAC. NEXTRAC is a federal advisory committee that provides recommendations to the NIH Director and a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies, which include, but are not restricted to, technologies surrounding advances in recombinant or synthetic nucleic acid research such as human gene transfer. These regulatory review committees and advisory groups and any new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions.

The FDA and EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. Adverse events in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates, which could require additional preclinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval. Similarly, the European Commission may issue new guidelines concerning the development and marketing authorization for gene therapies and require that we comply with these new guidelines, which could require additional preclinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval.

As we advance our product candidates, we are required to consult with these regulatory and advisory groups, and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

The FDA and EMA have recently released a series of final guidances and a draft guidance for consultation, which amongst other topics, included various aspects of gene therapy product development, review, and approval, including aspects relating to clinical and manufacturing issues related to gene therapy products. We cannot be certain whether future guidance will be issued and be relevant to, or have an impact on, our gene therapy programs or the duration or expense of any applicable regulatory development and review processes.

Our commercial product and product candidates and the process for administering our commercial product and 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 has 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.

There have been several adverse events and serious adverse events, or 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. 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 by the vectors, leading to malignant transformation of transduced cells. 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 European Medicines Agency. Furthermore, if we or others later identify undesirable side effects caused by our commercial product or 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 Strimvelis and any other products for which we obtain marketing approval and could significantly harm our business, prospects, financial condition and results of operations.

To date, most of the clinical trials for our product candidates were conducted as investigator-sponsored clinical trials using drug product manufactured at the 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 contract development and manufacturing organizations, or 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. 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 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 UCLA for OTL-101 with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. The bacteremia resolved on Day 3 without sequelae. We believe that our commercial manufacturing processes for OTL-101 and our other 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.

The interim data and ad hoc analyses summarized in this Annual Report are current as of the dates specified and are preliminary in nature. Our company-sponsored clinical trials of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and the investigator-sponsored clinical trials for OTL-102 for X-CGD, OTL-203 for MPS-I, OTL-201 for MPS-IIIa and OTL-300 for TDT are ongoing and not complete. Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

From time to time, we may publish interim data and/or ad hoc analyses from investigator-sponsored or company-sponsored clinical trials of our product candidates. Preliminary data and ad hoc analyses from these clinical trials may change as more 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 from time to time elect not to conduct subsequent interim analyses so as not to compromise the statistical analysis plan for the trial. Accordingly, our interim analyses do not include data subsequent to the cut-off date and may not be available until the next planned interim analysis. From time to time, preliminary data and ad hoc analyses might be presented, typically by academic investigators at scientific conferences or in scientific publications.

With respect to clinical trials conducted by our academic or other collaborators, such as University College London, UCLA, Telethon-OSR and GSK, we may not have access to the most recent clinical data or the clinical data available to us may otherwise be limited or incomplete. Interim data or ad hoc analyses from these clinical trials are not necessarily predictive of final results. Interim data or ad hoc analyses are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and/or more patient data become available to us. Interim, topline and preliminary data and ad hoc analyses also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data available to us or that we previously published. As a result, preliminary and interim data and ad hoc analyses should be viewed with caution until the final data are available. Material adverse changes in the final data compared to the preliminary or interim data or ad hoc analyses could significantly harm our business prospects.

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

For example, although sustained clinical activity has been observed in clinical trials to date for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, follow-up in each of 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 marketing approvals. 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 is limited data concerning long-term safety and efficacy following treatment with our product candidates. OTL-201 for MPS-III A, and OTL-202 for mucopolysaccharidosis type III-B, or MPS-III B, have not yet been tested in humans. These and any of our other product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in preclinical studies. Our product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical trials. There can be no assurance that any of these trials will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates. In addition, there can be no assurance that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.

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

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

We plan to submit any data available to us from compassionate use cases as part of any regulatory submission for the applicable product candidate. However, because these patients were not treated as part of a clinical trial regulatory framework and related requirements, regulatory authorities may not accept compassionate use data as sufficiently robust clinical evidence in support of our regulatory approval efforts, or they may find that the data submitted from our clinical trials are insufficient to support approval. Such decisions could materially and adversely affect our business, financial condition, results of operations and prospects.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity

from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with the required or desired characteristics, to complete our clinical trials in a timely manner. For example, due to the nature of the indications that we are initially targeting, patients with advanced disease progression may not be suitable candidates for treatment with our product candidates and may be ineligible for enrollment in our clinical trials. Therefore, early diagnosis in patients with our target diseases is critical to our success. Patient enrollment and trial completion is affected by factors including the:

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- safety profile, to date, of the product candidate under study;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases, including any required pretreatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- degree of progression of the subject's disease at the time of enrollment;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective subjects;
- 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 the 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 uncertain as to outcome. 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 IRB approval at each clinical trial site;
- delays in recruiting suitable patients to participate in our clinical trials;
- imposition of a clinical hold by regulatory agencies;
- failure by our academic partners, CROs, other third parties or us to adhere to clinical trial protocol and recordkeeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- the occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits;
or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues. In addition, if we make changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with, or later become subject to, labeling or a REMS (or equivalent requirement from a non-U.S. regulatory authority) that includes significant use or distribution restrictions or safety warnings, precautions, contraindications, drug interactions, or adverse events;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical trials to support comparability or approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a REMS (or equivalent requirement from a non-U.S. regulatory authority);
- be sued by competitors, patent holders, patients, or third parties; or
- experience damage to our reputation.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

We may elect to initiate a rolling BLA for our product candidates, in which case the FDA will not complete, and may delay initiating, its review of the BLA until we submit all of the required information.

A rolling BLA is an application process that allows us to submit the information required by the BLA in sections. The FDA will not complete, and may delay initiating, its review of our BLA until we submit all of the required information for a full BLA. If we are delayed or unable to provide this required information it could delay or prevent our ability to obtain regulatory approvals, as a result of which our business, prospects, financial condition and results of operations may suffer.

The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates. Before we submit our product candidates for marketing approval, the FDA and/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 for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS may not be sufficiently robust to support the submission of marketing approval for our product candidates. The FDA or EMA normally requires two registrational trials to approve a drug or biologic product, and thus the FDA or EMA may require that we conduct additional clinical trials of our product candidates prior to a BLA or MAA submission. The FDA or EMA typically does not consider a single registrational clinical trial to be adequate to serve as sufficient evidence to support a marketing authorization unless it is, among other things, well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and a confirmatory study would be practically or ethically impossible. Additionally, while the FDA recognizes the potential for natural history models to augment the need for placebo arms in trials for drugs that target very rare disease, 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.

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 practicable for ethical and other reasons. It is possible the FDA will not consider our comparisons to natural history data and, where available, historical transplant data, to provide clinically meaningful results. Additionally, even though OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS have achieved the primary endpoints in their respective ongoing registrational clinical trials, neither the FDA nor EMA have approved the primary endpoints and data in these trials and, therefore, it is still possible that the FDA or EMA may require us to conduct a second registrational trial, possibly involving a larger sample size or a different clinical trial design, particularly if the FDA or EMA does not find the results from these trials to be sufficiently persuasive to support a BLA or MAA submission, as applicable. 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 our BLA or MAA submission, as applicable.

In addition, data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other foreign regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. FDA may further refer our 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 SAEs involving our product candidates, changes in regulatory policy or changes in requirements during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

We expect that the FDA and EMA will assess the totality of the safety and efficacy data from our product candidates in reviewing any future BLA or MAA submissions. Based on this assessment, the FDA or EMA may require that we conduct additional preclinical studies or clinical trials prior to submitting or approving a BLA or MAA for our target indications.

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

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 were conducted outside the United States. For example, we do not yet have an IND open in the United States for OTL-200 for MLD, OTL-203 for MPS-I or OTL-300 for TDT. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, 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.

In addition, in order to commence a clinical trial in the United States, we are required to seek FDA acceptance of an IND for each of our product candidates. We cannot be sure any IND we submit to the FDA, or any similar CTA we submit in other countries, will be accepted. We may also be required to conduct additional preclinical testing prior to submitting an IND for any of our product candidates, and the results of any such testing may not be positive. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to a BLA submission and approval of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing our product candidates.

We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells, or HSCs, derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product and/or demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CDMOs. Failure to demonstrate such comparability could adversely affect our ability to secure regulatory approval for our product candidates, or could adversely affect the commercial viability of our product candidates if approved for use using only HSCs derived using bone marrow and/or fresh drug product.

To date, most of the patients who have been treated in clinical trials involving our product candidates received fresh drug product manufactured using HSCs derived from the patient's bone marrow at academic centers. We are currently evaluating our product candidates and plan to seek marketing approval using drug product that is manufactured at CDMOs using HSCs derived from either the patient's bone marrow or mobilized peripheral blood and using a procedure by which the gene-modified HSCs are cryopreserved in order to maintain the cellular material in suitable condition until it is thawed prior to being infused into the patient.

In those cases where clinical trials were conducted using vector and/or drug product manufactured at academic research centers, we will need to demonstrate comparability between vector and drug product manufactured by our CDMOs with vector and/or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another and in some 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 comparability analyses, preclinical studies and/or clinical trials before approving our product candidates using these production methods and processes. Moreover, we cannot be assured that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval of our product candidates using these production methods and processes. For example, both the FDA and the EMA has advised us that it will require clinical data using drug product that has been cryopreserved as part of our planned BLA and MAA submissions for OTL-103 for WAS. In addition, we are conducting a clinical trial at UCLA using a cryopreserved formulation of OTL-101 (with bone marrow as the cellular source). In this trial, one of the 10 patients treated with this formulation failed to engraft, although we do not believe engraftment failure was due to use of a cryopreserved formulation.

If the FDA, EMA or other regulatory authority does not accept our comparability data, 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. 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, our regulatory approval, if any, 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. Failure to demonstrate such comparability, or if we are required to conduct additional testing or additional clinical trials, potentially at additional sites, would adversely affect the commercial viability of our product candidates and may adversely affect our ability to generate revenue, as a result of which our business, prospects, financial condition and results of operations may suffer.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate and the approval may be for a more narrow indication than we seek.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

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 (such as pre-symptomatic MLD patients as opposed to symptomatic patients), 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), than we are seeking. If we are unable to obtain necessary regulatory approvals, or more limited regulatory approvals than we expect, our business, prospects, financial condition and results of operations may suffer.

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing such product candidate. While Strimvelis has been approved by the EMA, we have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process.

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

The process of obtaining marketing approvals, both in the United States and abroad, is expensive (the submission fee in the United States can be more than \$2.0 million and may be higher in the future), may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a drug candidate. Any marketing approval of our product candidates that we, or any future collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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

While we intend to seek designations for our product candidates with the FDA and comparable other 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-101 for ADA-SCID has received a Breakthrough Therapy designation from the FDA, OTL-103 for WAS a regenerative medicine advanced therapy, or RMAT, designation from the FDA and OTL-300 a Priority Medicines, or PRIME, designation from EMA, but there can be no assurance that we will successfully obtain such designation for any of our other product candidates. In addition, while such designations could expedite the development or approval process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

For example, we may seek a Breakthrough Therapy designation for some of our other product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

In addition, we may seek RMAT designation for some of our other product candidates. An RMAT is defined as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. The RMAT program is intended to facilitate efficient development and expedite review of RMATs, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. A BLA for an RMAT may be eligible for priority review or accelerated approval. An RMAT may be eligible for priority review if it treats a serious condition, and, if approved would provide a significant improvement in the safety or effectiveness of the treatment of the condition. An RMAT may be eligible for accelerated approval through (1) surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit or (2) reliance upon data obtained from a meaningful number of sites. Benefits of such designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. RMAT designation is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a RMAT, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of RMAT designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as for RMAT designation, the FDA may later decide that the biological products no longer meet the conditions for qualification.

In addition, the FDA has granted Rare Pediatric Disease designation to Strimvelis, OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and OTL-201 for MPS-III A, and we may seek Rare Pediatric Disease designation for some of our other product candidates. The FDA defines a “rare pediatric disease” as a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making in the U.S. a drug for such disease or condition will be 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 until September 30, 2020, with potential for PRVs to be granted until 2022. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and OTL-201 for MPS-III A and qualify for such a PRV, the program may no longer be in effect at the time or the value of any such PRV may decrease such that we are may not be able to realize the benefits of such PRV.

In addition, we may seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA approval. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

We may seek priority review designation for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, in particular if such product candidate has received a Breakthrough Therapy designation or RMAT designation, the FDA may decide not to grant it. Moreover, a priority review designation does not result in expedited development and does not necessarily result in expedited regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

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

We have sought and received orphan drug designation for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-III A from the FDA and EMA and for OTL-300 for TDT from the EMA, but we may be unable to obtain orphan drug designation for our other product candidates and, even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

We have sought and received orphan drug designation for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-III A from the FDA and EMA and for OTL-300 for TDT from the EMA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our 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 European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, 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.

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

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

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the European Union took effect on January 31, 2020 (the "Exit Day"). A post-Brexit transition period started on the Exit Day and is scheduled to expire on December 31, 2020. During the transition period most laws of the European Union continue to apply to the United Kingdom while the future relationship between the United Kingdom and the European Union is formally negotiated based on terms set out in the political declaration on the framework for the future relationship made by the United Kingdom and European Union negotiators. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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, when doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the Committee for Medicinal Products for Human Use, or 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;
- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data is still required.

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

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

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

Strimvelis and any of our product candidates for which we obtain regulatory approval will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. 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 European Union, the advertising and promotion of our products are subject to European Union laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual European Union 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 European Union. The applicable laws at European Union level and in the individual European Union 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 European Union 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 European Union 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 European Union laws and the related national laws of individual European Union Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

In addition, European Union legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that EMA and the competent authorities of the European Union Member States have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct a burdensome collection of data regarding the risks and benefits of marketed products and may be required to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical trials, which may be time-consuming and expensive and could impact our profitability. Non-compliance with such obligations can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

We face significant competition in our industry and there can be no assurance that 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.

We rely primarily on know-how and trade secret protection for aspects of our proprietary technologies, our commercial product Strimvelis and our product candidates. We do not have any issued patents covering our commercial product Strimvelis or our product candidates, and only one patent family with patent applications pending in the United States and Europe with patent claims directed to our OTL-101 product candidate and its use in the treatment of ADA-SCID. 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 product or our product candidates, and this may expose us to competition from other biopharmaceutical companies, particularly those companies that possess greater financial resources and more mature product candidate development, manufacturing, marketing and distribution resources than we do. Although our product candidates, if approved, may be eligible for marketing and/or data exclusivities in, for example, the United States and Europe, these exclusivities would not prevent another biopharmaceutical company from conducting its own clinical trials to develop and seek regulatory approval of a competitive product. We are not the only company that is developing and commercializing products using a lentiviral-based autologous *ex vivo* gene therapy approach, and these competitive approaches may be comparable or superior to our approach. One or more of these companies may seek to develop products that compete directly with our commercial product or one or more of our product candidates, the result of which could have a material adverse effect on our business.

bluebird bio is commercializing LentiGlobin in Europe, marketed as Zynteglo, a lentiviral-based autologous *ex vivo* gene therapy for TDT, after receiving a conditional marketing authorization from the European Commission in June 2019 for the treatment of adolescents and adults with TDT and a non- β_0/β_0 genotype. bluebird bio has initiated a rolling BLA in the United States for LentiGlobin for the treatment of TDT and has publicly announced its intention to complete the BLA submission in the first half of 2020. This product candidate has been granted orphan drug status by both the FDA and EMA for the treatment of beta-thalassemia, Fast Track Designation by the FDA for the treatment of beta-thalassemia major, Breakthrough Therapy Designation by the FDA for the treatment of transfusion-dependent patients with beta-thalassemia major and Priority Medicines (PRIME) designation by the EMA for the treatment of TDT. These designations may delay or prevent our ability to commercialize OTL-300 for TDT for the applicable periods in the European Union and in the United States if the product candidate receives marketing approvals in the respective territories.

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.

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

As part of our growth strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates for ADA-SCID, MLD, WAS, X-CGD, MPS-I, MPS-III A and TDT. We may spend several years completing our development of any particular current or future product candidates, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential than OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS or our other product candidates. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

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

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as bone marrow transplantation or enzyme replacement therapy. We have not yet succeeded and 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. For example, although we acquired Strimvelis, we have not yet obtained regulatory approval to sell any of our other product candidates based on our therapeutic approach. Accordingly, our focus on treating rare diseases may not result in the discovery and development of commercially viable products.

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

Risks related to manufacturing and supply

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial product 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. 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, 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 scales for our clinical trials and current and initial commercial demands, if 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 have in-house capabilities. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

We have limited experience manufacturing our product candidates. On December 13, 2018, we entered into a long-term lease agreement for our own gene therapy manufacturing facility in Fremont, California. We are in the process of building out this manufacturing facility to develop cGMP manufacturing capacity for both lentiviral vector and cryopreserved cell therapy products. We may be unable to produce clinical or commercial viral vectors or Strimvelis or our product candidates or meet demand to support a clinical trial or a commercial launch for our product candidates. Any such failure 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 us or 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 we or 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 potential future 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 our own facility, or the facility of a CDMO, 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 and, therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our or 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 we or 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.

We are in the process of building out our Fremont, California manufacturing facility for the manufacture of our viral vectors and product candidates, which will be costly, time-consuming, and which may not be successful.

We have entered into a lease for a 152,995 square foot facility located in Fremont, California to serve as an alternative or an addition to our reliance on CDMOs, for the manufacture of our viral vectors and product candidates. We plan to renovate and retrofit this facility for the manufacture of lentiviral vectors and product candidates. We expect that development of our own manufacturing facility will provide us with enhanced control of material supply for both clinical trials and commercialization, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in building a manufacturing facility and may never be successful in developing our own manufacturing capabilities. Furthermore, we will need to hire additional personnel to manage our operations and facilities and develop the necessary infrastructure to continue the development, and eventual commercialization, if approved, of our product candidates. We, as a company, have no previous experience in setting up, building or eventually managing a manufacturing facility. If we failed to select the correct location, or if we fail to complete the planned renovation and retrofit of our Fremont, California facility in an efficient manner, or fail to recruit the required personnel and generally manage our growth effectively, the development and production of our viral vectors and product candidates could be curtailed or delayed. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

We also may encounter problems hiring and retaining the experienced technical, quality control, quality assurance and manufacturing personnel needed to operate our manufacturing processes and facilities, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements.

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 manufacturing facility or satisfying manufacturing-related regulatory requirements.

Operating our own manufacturing facility in Fremont, California requires significant resources, and we do not have experience as a company in managing a manufacturing facility and complex supply chain. In part because of this lack of experience, we cannot be certain that our manufacturing plans will be completed on time, if at all, or if manufacturing of product candidates from our own manufacturing facility for our planned clinical trials will begin or be completed on time, if at all. In part because of our inexperience, we may have unacceptable or inconsistent product quality success rates and yields, and we may be unable to maintain adequate quality control, quality assurance, manufacturing, technical or other qualified personnel. In addition, if we switch from our current CDMOs to our own manufacturing facility for one or more of our product candidates in the future, we may need to conduct additional preclinical, analytical or clinical trials to bridge our modified product candidates to earlier versions. Failure to successfully renovate and operate our planned manufacturing facility could adversely affect the commercial viability of our product candidates.

In addition, the FDA, the 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, the 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. Patients' cellular source material must be collected, prepared, stored and transported from the clinical collection site to the manufacturing facility and the cryopreserved drug product must be returned to the clinical site 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 qualified 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 patients' 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 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, other events or held up at a customs point, 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, held up at a customs point 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.

Any of the above events, should they happen, could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Our gene therapies are for autologous use only. Therefore, if a drug product is administered to the wrong patient, the patient could suffer harm.

Our gene therapies are autologous, so they must be administered back only to the patient from which the cellular source material was collected. While we implement specific identifiers, lot numbers and labels with cross checks for our products and operations from collection of cellular source material, through manufacture of drug product, transport of product to the clinical site up to thawing and administration of the product, it is possible that a product may be administered into the wrong patient. If an autologous gene therapies were to be administered into the wrong patient, the patient could suffer harm, including experiencing a severe adverse immune reaction and this event, should it happen, could adversely affect our business, financial condition, results of operations and prospects.

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

Given the nature of biologics manufacturing, there is a risk of microbial contamination. Any microbial contamination could adversely affect our ability to produce, release or administer our gene therapies on schedule and could, therefore, harm our results of operations and cause reputational damage. Additionally, although our gene therapies are tested for microbial contamination prior to release, if a contaminated product was administered to a patient, it could result in harm to the patient.

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

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

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

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

We may also enter into additional collaborations in the future. We have limited control over the amount and timing of resources that our current and future collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our and our collaborators' abilities to successfully perform the functions assigned to each of us in these arrangements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator is responsible could be harmful to the public perception and prospects of our gene therapy platform.

We may enter into additional collaborations with third parties in the future. 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 and/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 the collaboration. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report apply to the activities of our collaborators.

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of our 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 is time-consuming and complex. Our ability to reach a definitive collaboration agreement 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 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.

Until such time as we complete the build out of our Fremont, California manufacturing facility and establish that it has been properly commissioned to comply with cGMP requirements, we will not be able to independently manufacture material for our planned clinical programs or our commercial supply, Strimvelis or any other product for which we obtain marketing approval. We currently rely on our CDMOs and in some cases academic partners for the production of our viral vectors and product candidates for our ongoing registrational and clinical trials and preclinical studies. For future clinical trials and for products for which we obtain marketing approval, we intend to utilize materials manufactured by CDMOs. If our academic partners or these CDMOs do not successfully carry out their contractual duties, meet expected deadlines or manufacture our viral vector and product candidates in accordance with regulatory requirements or if there are disagreements between us and our academic partners or these CDMOs, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support approval of our product candidates or the FDA, EMA or other regulatory agencies may refuse to accept our clinical or preclinical data. In such instances, we may need to enter into an appropriate replacement third-party relationship, which may not be readily available or available on acceptable terms, which would cause additional delay or increased expense prior to the approval of our product candidates and would thereby 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 for the production of 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 are entitled to terminate their engagements with us. If we need to enter into alternative arrangements, it could delay our development activities. Our reliance on our CDMOs for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations.

In addition to our current CDMOs, we may rely on additional third parties to manufacture our viral vectors and or drug products in the future and to perform quality testing, and reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize any of our product candidates. Some of these events could be the basis for FDA, EMA or other regulatory authority action, including injunction, recall, seizure or total or partial suspension of product manufacture.

We rely on third parties, including independent clinical investigators and CROs, to conduct and sponsor some of the clinical trials of our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for our product candidates.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our preclinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing preclinical and clinical programs. For example, OTL-300 for TDT is currently being investigated in an ongoing academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy, and OTL-102 for X-CGD is currently being investigated in ongoing academic-sponsored clinical trials at Boston Children's Hospital, the NIH and UCLA in the United States, and GOSH in Europe. Additionally, our registrational trial of OTL-101 for ADA-SCID was initially sponsored by UCLA. While we will have agreements governing the activities of our academic partners and CROs, we will control only certain aspects of their activities and have limited influence over their actual performance.

Nevertheless, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GLP and GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or 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. If we fail to exercise adequate oversight over any of our academic partners or CROs or if we or any of our academic partners or CROs do not successfully carry out their 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, or for any other reasons, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure that upon a regulatory inspection of us, our academic partners or our CROs or other third parties performing services in connection with our clinical trials, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under applicable cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

We do not control the design or conduct of the academic-sponsored trials, and it is possible that the FDA or EMA will not view these academic-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. Such arrangements provide us certain information rights with respect to the academic-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the academic-sponsored trials. However, we do not have control over the timing and reporting of the data from academic-sponsored trials, nor do we own the data from the academic-sponsored trials. If we are unable to confirm or replicate the results from the academic-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of OTL-300 for TDT, OTL-102 for X-CGD, OTL-203 for MPS-I, OTL-201 for MPS-III 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 firsthand knowledge we might have gained had the academic-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or EMA may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these academic-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these academic-sponsored trials. If so, the FDA or EMA may require us to obtain and submit additional preclinical, manufacturing, or clinical data.

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

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and drug products. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing CDMOs for our viral vectors and drug product, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials, including in some cases critical raw materials used in the manufacture thereof, must be manufactured in accordance with cGMP. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our viral vectors or product candidates that may not be detectable in final product testing. We or our CDMOs must supply all necessary documentation in support of a BLA or MAA on a timely basis and must adhere to the FDA's and EMA's cGMP and other applicable regulations that are enforced through facilities inspection programs. Some of our CDMOs have not produced a commercially-approved product and have never been inspected by the FDA or other regulatory body. Our quality systems and the facilities and quality systems of some or all of our CDMOs must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our viral vector or drug product or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted.

If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our CDMOs fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals of our product candidates or commercialization of our commercial product or product candidates, if approved, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our preclinical studies and clinical trials may be delayed.

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

We currently depend on a limited number of suppliers and, in some instances, a sole supplier, for some of the components and equipment necessary for the production of our viral vectors and drug product. We cannot be sure that these suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a sole or a limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components, and in some cases, no alternatives. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. 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; 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 product 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 them. 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

We currently have limited sales and marketing capabilities. If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates that may be approved, we may not be successful in commercializing our product candidates if and when approved, and we may be unable to generate any product revenue.

If our product candidates are approved for commercialization, we currently intend to seek to commercialize them in the United States and Europe directly with specialized teams, given the relative rarity of the indications we are targeting. We currently have a limited marketing and sales team for the marketing, sales and distribution of our commercial product and our product candidates, if approved. In order to commercialize Strimvelis and OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if approved, or any of our other product candidates that may be approved, we must build, on a territory-by-territory basis, marketing, sales, distribution, managerial and other capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a commercial organization is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- the inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product that we may develop;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market and sell any product candidates that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates.

If we are unable to expand our market development capabilities or enter into agreements with third parties to market and sell any of our product candidates for which we obtain marketing approval, we will be unable to generate any product revenue.

To successfully commercialize any products that may result from our development programs, we need to continue to expand our market development capabilities, either on our own or with others. The development of our own market development effort is, and will continue to be, expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may enter into collaborations regarding any approved product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded sales, distribution and marketing operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates, if approved. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for primary immune deficiencies, inherited metabolic and neurodegenerative genetic disorders and rare inherited blood 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 may prove to be incorrect, and new studies may reduce the estimated incidence or prevalence of these diseases. Patient identification efforts also influence the ability to address a patient population. If efforts in patient identification are unsuccessful or less impactful than anticipated, we may not address the entirety of the opportunity we are seeking. As a result, the number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, payors and others in the medical community.

Even if we obtain any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and payors accepting gene therapy products in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors and others in the medical community. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

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

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

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

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve market approval. In the United States and markets in other countries, patients generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments, such as stem cell transplants. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be covered and paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other payors. If coverage and adequate reimbursement is not available, or is 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. 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.

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, as the CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow the CMS to a substantial degree. It is difficult to predict what the CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Factors payors consider in determining reimbursement are based on whether the product is:

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

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenues from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. Some countries may also require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our product candidates. Historically, products launched in the European Union do not follow price structures of the U.S. and generally prices tend to be significantly lower.

Moreover, efforts by governmental and payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

We are targeting rare diseases for which the patient populations are relatively small. In addition, treatment with any of our product candidates involves only a single administration. As a result, the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. It is possible that commercially available products may serve as a reference price that, for various reasons, may be lower than the price we need to obtain for our product candidates. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates, if approved.

Healthcare legislative reform measures and constraints on national budget social security systems may have a material adverse effect on our business and results of operations.

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

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision that decreased the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, commonly referred to as the "individual mandate," to \$0, effective January 1, 2019. On December 14, 2018, a federal district court in Texas ruled the individual mandate is a critical and inseparable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional, and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. Pending review, the ACA remains in effect, but it is unclear at this time what effect the latest ruling will have on the status of the ACA.

Further, since January 2017, President Trump signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse

insurers under the ACA. The Trump administration concluded that cost-sharing reduction payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until those appropriations are made. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payers who argued were owed to them. This was appealed to the U.S. Supreme Court, which heard arguments on December 10, 2019. We cannot predict how the U.S. Supreme Court will rule. The effects of this gap in reimbursement on third-party payers, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. In December 2018, the CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of the federal district court litigation regarding the method CMS uses to determine this risk adjustment. In addition, CMS published a final rule that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Congress may consider other legislation to replace elements of the ACA.

Additionally, in January 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. However, on December 20, 2019, President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future. Further, the BBA, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” Congress also could consider subsequent legislation to replace elements of the ACA that are repealed. Thus, the full impact of the ACA, any law replacing elements of it, and the political uncertainty surrounding any repeal or replacement legislation on our business remains unclear. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and will remain in effect through 2029 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration’s budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 and 2020 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a “Blueprint”, or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. The Department of Health and Human Services (HHS) has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS’s policy change that was effective January 1, 2019. While a number of proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on September 25, 2019, the Senate Finance Committee introduced the Prescription Drug Pricing

Reduction Action of 2019, a bill intended to reduce Medicare and Medicaid prescription drug prices. The proposed legislation would restructure the Part D benefit, modify payment methodologies for certain drugs, and impose an inflation cap on drug price increases. An even more restrictive bill, the Lower Drug Costs Now Act of 2019, was introduced in the House of Representatives on September 19, 2019, and would require HHS to directly negotiate drug prices with manufacturers. The Lower Drugs Costs Now Act of 2019 has passed out of the House and was delivered to the Senate on December 16, 2019. However, it is unclear whether either of these bills will make it through both chambers and be signed into law, and if either is enacted, what effect it would have on our business. Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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

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

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

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. In particular, 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. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death seen in other trials using other vectors. 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/or 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 on May 30, 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, which could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

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

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and continue to build a commercial infrastructure to support commercialization of Strimvelis and any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

Our future results will suffer if we do not effectively manage our expanded operations as a result of our acquisition of Strimvelis, OTL-200 for MLD, OTL-103 for WAS, OTL-203 for MPS-I and OTL-300 for TDT or of future acquisitions or strategic transactions.

We acquired worldwide rights to Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDT in April 2018 pursuant to the GSK Agreement, and worldwide rights to OTL-203 for MPS-I in May 2019 pursuant to an exclusive licensing agreement with Telethon-OSR. The GSK Agreement significantly changed the composition of our operations, markets and product candidate mix, and we are continuing to adapt our organization to support these acquisitions. Our future success depends, in part, on our ability to continue to address these changes, and, where necessary, to attract and retain new personnel that possess the requisite skills called for by these changes.

Our failure to adequately address the financial, operational or legal risks of our acquisition of the rights to Strimvelis, OTL-200 for MLD, OTL-103 for WAS, OTL-203 for MPS-I and OTL-300 for TDT, or any future acquisitions, license arrangements, other strategic transactions could harm our business. Financial aspects of such future transactions that could alter our financial position, or operating results include:

- use of cash resources;
- higher than anticipated acquisition costs and expenses;

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

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

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

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

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 comply with the regulations of the FDA, EMA or of other foreign regulatory authorities, provide accurate information to the FDA, EMA and other foreign regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or 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.

We are subject to the U.K. 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 federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties;
- the federal civil and criminal false claims laws and civil monetary penalty laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery;

- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;
- The U.S. federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- Many state laws govern the privacy of personal information in specified circumstances, 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. While clinical trial data and information governed by HIPAA are currently exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope.

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 payer. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute and False Claims Act, and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the European Union General Data Protection Regulation, which became effective May 2018 also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

In the event we decide to conduct clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Economic Area, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR includes restrictions on cross-border data transfers. 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. Further, the United Kingdom's vote in favor of exiting the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated, nor is it clear when Brexit will occur.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge and may not comply under one or more of such laws, regulations, and guidance. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive stock 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.

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

The use of our product candidates in clinical trials and the sale of Strimvelis or any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. 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 each time we commercialize an additional product; however, 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.

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, 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 U.K. 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;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, fires and public health epidemics and pandemics.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business, which could reduce the price of our ADSs.

In June 2016, a majority of the eligible members of the electorate in the United Kingdom voted to withdraw from the European Union in a national referendum, commonly referred to as Brexit. The withdrawal of the United Kingdom from the European Union took effect on January 31, 2020 (the "Exit Day"). A post-Brexit transition period started on the Exit Day and is scheduled to expire on December 31, 2020. During the transition period most laws of the European Union continue to apply to the United Kingdom while the future relationship between the United Kingdom and the European Union is formally negotiated based on terms set out in the political declaration on the framework for the future relationship made by the United Kingdom and European Union negotiators. If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms, barrier-free access between the United Kingdom and other European Member States or among the European Economic Area, or EEA, overall could be diminished or eliminated.

The uncertainty concerning the United Kingdom's legal, political and economic relationship with the European Union after Brexit may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise) beyond the date of Brexit.

These developments, or the perception that any of them could occur, have had, and may continue to have, a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our ADSs. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which European Union rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital.

If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms, or if other EU Member States pursue withdrawal, barrier-free access between the United Kingdom and other EU Member States or among the EEA overall could be diminished or eliminated. The long-term effects of Brexit will depend on any agreements (or lack thereof) between the United Kingdom and the European Union and, in particular, any arrangements for the United Kingdom to retain access to European Union markets either during a transitional period or more permanently.

Such a withdrawal from the European Union is unprecedented, and it is unclear how the United Kingdom's access to the European single market for goods, capital, services and labor within the European Union, or single market, and the wider commercial, legal and regulatory environment, will impact our United Kingdom operations and customers. Our United Kingdom operations could be disrupted by Brexit, particularly if there is a change in the United Kingdom's relationship to the single market.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of the United Kingdom's withdrawal from the European Union, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members, which may result in increased trade barriers that could make our doing business in the European Union and the EEA more difficult. Furthermore, there are likely to be changes to the way in which marketing approvals are granted in the United Kingdom and what, if any, role the EMA may have in the approval process, which could add time and expense to the process by which our product candidates receive and maintain regulatory approval in the United Kingdom and across the EEA in the future. Even prior to any change to the United Kingdom's relationship with the European Union, the announcement of Brexit has created economic uncertainty surrounding the terms of Brexit and its consequences which could adversely affect our business, revenue, financial condition, results of operations and could adversely affect the market price of our ADSs.

We may be adversely affected by earthquakes, fires or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes, fires or other natural disasters, including health epidemics and pandemics, could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects, particularly as we expand operations to areas known to be prone to such disasters, such as California. If a natural disaster, fire, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters or other facilities, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business, financial condition, results of operations and prospects.

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 based in the United Kingdom, we source research and development, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

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

We currently have \$25.0 million of principal indebtedness outstanding under our senior term facilities agreement dated as of May 24, 2019, between us, as borrower, and MidCap Financial (Ireland) Limited, as lender, or the Credit Facility. We have the ability to borrow up to an additional \$50.0 million in the future under the Credit Facility upon satisfaction of certain conditions. Our existing indebtedness and any additional indebtedness we may incur could require us to divert funds identified for other purposes for debt service and impair our liquidity position.

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

- increasing our vulnerability to general adverse economic and industry conditions or increased interests rates;
- reducing the availability of 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 our 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.

Our Credit Facility contains usual and customary restrictive covenants relating to the operation of our business, including restrictions on our ability:

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

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

National and international regulators and law enforcement agencies have conducted investigations into a number of rates or indices known as “reference rates.” Actions by such regulators and law enforcement agencies may result in changes to the manner in which certain reference rates are determined, their discontinuance, or the establishment of alternative reference rates. In particular, in July 2017, the Chief Executive of the U.K. Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA will no longer persuade or compel banks to submit rates for the calculation of LIBOR after 2021. Such announcement indicates that the continuation of LIBOR on the current basis cannot and will not be guaranteed after 2021. As a result, it appears highly likely that LIBOR will be discontinued or modified by 2021.

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

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

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 damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. 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 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.

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 U.S. patents relating to the lentiviral vectors used in the manufacture or use of our product candidates. If these patent rights were enforced against us, we believe that we have defenses against any such action, including that these patents would not be infringed by our product candidates and/or that these patents are not valid. However, if these patents were enforced against us and defenses to such enforcement were unsuccessful, unless we obtain a license to these patents, which may not be available on commercially reasonable terms, or at all, we could be liable for damages and precluded from commercializing any products and product candidates that were ultimately held to infringe these patents, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We are highly dependent on intellectual property and data licensed from third parties to develop and commercialize our products and product candidates and our development and commercialization abilities are subject, in part, to the terms and conditions of licenses granted to us by such third parties.

We are highly dependent on the intellectual property and data licensed to us by third parties that are important or necessary to the development of our technology and products and product candidates, including technology related to the manufacture and use of our products and product candidates. In particular, we do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis or any of our lead product candidates. We have in-licensed one U.S. patent application and a counterpart European patent application, know-how and data from UCLA and UCL Business plc, or UCLB, relating to OTL-101 for ADA-SCID. In addition, we have in-licensed certain know-how and data from GSK and Telethon-OSR, relating to Strimvelis, OTL-103 for WAS, OTL-200 for MLD, and OTL-300 for TDT. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

Although our license rights from The Regents of the University of California, University College London, GSK, and Telethon-OSR, are exclusive, they are limited to particular fields, such as ADA-SCID, MLD, WAS or TDT, and are subject to certain retained rights. Absent an amendment or additional agreement, we may not have the right to use the in-licensed intellectual property, data, or know-how for one of our programs in another program. Furthermore, the licenses (including sublicenses) that we have or may enter into in the future may not provide rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology, products and product candidates. As a result, we may not be free to commercialize certain of our products or product candidates in fields or territories of interest to us. Furthermore, if the licenses are not exclusive in territories of interest to us, we may be unable to prevent competitors from developing and commercializing competitive products in territories included in our licenses. Licenses (including sublicenses) to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business.

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

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected products and product candidates. Termination of our license agreements or reduction or elimination of our rights under them may result in our having to negotiate a new or reinstated agreement, which may not be available to us on equally favorable terms, or at all, which may mean we are unable to develop or commercialize the affected product or product candidate or cause us to lose our rights under the agreement. Any of the foregoing could have a material adverse effect on our business.

If we are unable to obtain and maintain patent and other intellectual property protection for our products and product candidates, or if the scope of the patent and other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. We currently do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis or any of our lead product candidates. In addition, the U.S. patent application and its counterpart European patent application we have in-licensed from The Regents of the University of California and University College London relating to OTL-101 are at a very early stage. Many of our products and product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all. Our or our licensors' failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties, in particular, other established and better financed gene therapy companies having established development, manufacturing and distribution capabilities, to make competing products or impact our ability to develop, manufacture and market our products and product candidates, even if approved, on a commercially viable basis, if at all, which could have a material adverse effect on our business.

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

We currently do not own any issued patents related to Strimvelis or our lead product candidates. Certain intellectual property related to Strimvelis and all of our product candidates are in-licensed from third parties but we have not in-licensed any issued patents related to Strimvelis or any of our product candidates. In certain situations and as considered appropriate, we and our licensors have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States relating to current and future products and product candidates that are important to our business. However, we cannot predict whether the patent applications currently being pursued will issue as patents, whether the claims of any resulting patents will provide us with a competitive advantage or prevent competitors from designing around our claims to develop competing technologies in a non-infringing manner, or whether we will be able to successfully pursue patent applications in the future relating to our current or future products and product candidates. Moreover, the patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Furthermore, we, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to seek additional patent protection.

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

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

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

Filing, prosecuting, maintaining, defending and enforcing patents on products and product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. Although our license agreement with UCLA and UCLB pertaining to OTL-101 grants us worldwide rights, and our currently in-licensed patent family relating to OTL-101 has a European patent application, 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 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, further, 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 one of our licensing partners or we 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.

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 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.

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, including rights licensed to us by UCLA relating to our OTL-101 product candidate for ADA-SCID, may have been generated through the use of U.S. government and California 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.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe, misappropriate or otherwise violate patents, trademarks, copyrights or other intellectual property that we own or 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 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, the court may decide not to grant an injunction against the offender and instead award only monetary damages, which may or 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.

Changes in patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products and product candidates.

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

The patent positions of companies engaged in the development and commercialization of biologics are particularly uncertain. Two cases involving diagnostic method claims and “gene patents” have been decided by the Supreme Court of the United States, or 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 has held in *Myriad* that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter, the result of which could have a material adverse effect on our business.

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.

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 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.

Risks related to ownership of our securities

The market price of our ADSs may be highly volatile, and may fluctuate due to factors beyond our control.

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

- adverse results or delays in preclinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by 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;
- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

In addition, companies trading in the stock market in general, and The Nasdaq Global Select Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our ADSs, regardless of our actual operating performance.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant securities price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

If securities or industry analysts do not continue to publish research or publish inaccurate or unfavorable research about our business, our ADS price and trading volume could decline.

The trading market for our ADSs depends in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. In the event one or more analysts downgrade our ADSs or change their opinion of our ADSs, our ADS price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our ADS price or trading volume to decline.

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

Based upon our ordinary shares outstanding as of December 31, 2019, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 41% of our ordinary shares and ADSs. Depending on the level of attendance at our general 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 general meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our general 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, the approval of certain significant corporate transactions and amendments to our Articles of Association. 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 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. See “—A significant portion of our total outstanding ordinary shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our ADSs to drop significantly.”

Holder 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.

Holder of ADSs may be subject to limitations on the transfer of their ADSs and the withdrawal of the underlying ordinary shares.

ADSs are transferable on the books of the depositary. However, the depositary may close its books at any time or from time to time when it deems expedient in connection with the performance of its duties. The depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary think it is advisable to do so because of any requirement of law, government or governmental body, or under any provision of the deposit agreement, or for any other reason, subject to the right of ADS holders to cancel their ADSs and withdraw the underlying ordinary shares. Temporary delays in the cancellation of the holder’s ADSs and withdrawal of the underlying ordinary shares may arise because the depositary has closed its transfer books or we have closed our transfer books, the transfer of ordinary shares is blocked to permit voting at a shareholders’ meeting or we are paying a dividend on our ordinary shares. In addition, ADS holders may not be able to cancel their ADSs and withdraw the underlying ordinary shares when they owe money for fees, taxes and similar charges and when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to ADSs or to the withdrawal of ordinary shares or other deposited securities.

We are entitled to amend the deposit agreement and to change the rights of ADS holders under the terms of such agreement, or to terminate the deposit agreement, without the prior consent of the ADS holders.

We are entitled to amend the deposit agreement and to change the rights of the ADS holders under the terms of such agreement, without the prior consent of the ADS holders. We and the depository may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us or to the depository. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depository. In the event that the terms of an amendment are materially disadvantageous to ADS holders, ADS holders will only receive 30 days' advance notice of the amendment, and no prior consent of the ADS holders is required under the deposit agreement. Furthermore, we may decide to direct the depository to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our ordinary shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility will terminate, ADS holders will receive at least 30 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but will have no right to any compensation whatsoever.

ADSs holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that, to the fullest extent permitted by law, holders and beneficial owners of ADSs irrevocably waive the right to a jury trial of any claim they may have against us or the depository arising out of or relating to the ADSs or the deposit agreement.

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depository opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the United States Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs.

If any holders or beneficial owners of ADSs bring a claim against us or the depository in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, such holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and / or the depository. If a lawsuit is brought against us and/or the depository under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

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

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

Except as described in this Annual Report and the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the depository to vote the ordinary shares underlying their ADSs. Otherwise, holders of ADSs will not be able to exercise their right to vote unless they withdraw the ordinary shares underlying their ADSs to vote them in person or by proxy in accordance with applicable laws and regulations and our Articles of Association. Even so, ADS holders may not

know about a meeting far enough in advance to withdraw those ordinary shares. If we ask for the instructions of holders of the ADSs, the 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.

A significant portion of our total outstanding ordinary shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our ADSs to drop significantly.

Sales of a substantial number of our ADSs in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. As of December 31, 2019, we have outstanding 96,923,729 ordinary shares. The holders of up to 24,699,842 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, 6,267,916 ordinary shares reserved for issuance upon the exercise of existing options outstanding as of December 31, 2019 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.

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 all or a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether U.K. courts would entertain original actions brought in the United Kingdom against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of the United Kingdom as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that certain requirements are met. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement.

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

As a result of the loss of our foreign private issuer status, we are now required to comply with the Exchange Act's domestic reporting regime, which will cause us to incur significant legal, accounting and other expenses.

As of June 28, 2019, we determined that we no longer qualify as a "foreign private issuer" as such term is defined in Rule 405 under the Securities Act, which means that we are required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. As of January 1, 2020, we have been required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We will have been required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. As a result of such compliance, we expect that the regulatory and compliance costs to us under U.S. securities laws will be higher than the cost we incurred as a foreign private issuer and therefore, we expect that the loss of foreign private issuer status will increase our legal and financial compliance costs and will make some activities highly time consuming and costly. We also expect that compliance with the rules and regulations applicable to U.S. domestic issuers will make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our Board of Directors. In addition, our officers and directors are no longer exempt from the reporting and "short-swing" profit recovery provisions of Section 16 of the Exchange Act and related rules with respect to their purchase and sales of our securities.

Because we are no longer an "emerging growth company," as defined in the JOBS Act, we must incur additional expenses and devote increased management time to compliance with additional disclosures that are applicable to companies that are not emerging growth companies.

From our initial public offering until December 31, 2019, we were an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). While we were an emerging growth company, we were permitted to take advantage of reduced regulatory and reporting requirements that are otherwise generally applicable to public companies. These included, without limitation, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding non-binding advisory votes on executive compensation and golden parachute payments. Because we ceased to be an emerging growth company effective as of December 31, 2019, we expect to incur additional expenses and to devote increased management time toward ensuring compliance with those requirements applicable to companies that are not emerging growth companies.

In particular, beginning with this Annual Report on Form 10-K, our independent registered public accounting firm is required to provide an annual attestation report, in compliance with Section 404 of the Sarbanes-Oxley Act, regarding the effectiveness of our internal control over financial reporting. See "—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."

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, we are required to furnish a report by our management on our internal control over financial reporting. As a large-accelerated filer, we also require an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In order to achieve and maintain compliance with Section 404, we have documented and evaluated our internal control over financial reporting, which is both costly and challenging. In this regard, we continue to dedicate internal resources, have engaged outside consultants and adopted a detailed work plan to continually assess and document the adequacy of internal control over financial reporting, taken steps to improve control processes as appropriate, validated through testing that controls are functioning as documented and have implemented a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk in any given year that we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. Moreover, if 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 common stock could be negatively affected, and we could become subject to investigations by the SEC or other regulatory authorities or to stockholder litigation, which could have an adverse impact on the market price of our common stock and cause us to incur additional expenses.

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 previously identified material weaknesses in our internal control over financial reporting. We may identify future material weaknesses in our internal control over financial reporting. If we are unable to remedy these material weaknesses, or if we fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our ADS price.

Our management previously identified deficiencies that were concluded to represent a material weakness in our internal control over financial reporting where we did not design or implement sufficient controls and other review procedures performed by personnel familiar with U.S. GAAP to evaluate the recognition and accrual of research and development related expenses and reimbursements. A material weakness is defined as a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected and corrected on a timely basis.

In response to the material weakness, we have enhanced our controls around the recognition and accrual of research and development related expenses and reimbursements, including:

- Hiring a third-party professional accounting consulting firm to assist in establishing and implementing appropriate financial reporting policies, processes and controls over the recognition and accrual of research and development related expenses and reimbursements;
- Documenting the step-by-step processes and controls necessary to ensure that the recognition and accrual of research and development related expenses and reimbursements are accounted for in accordance with U.S. GAAP;
- Enhancing documentation and controls supporting the recognition and accrual of research and development related expense and reimbursements; and
- Providing increased oversight and review of the accrual of research and development related expense and reimbursements by personnel familiar with U.S. GAAP.

These controls around our oversight and review of the accrual of research and development related expenses and reimbursements have operated for a sufficient period of time, and management's evaluation of such controls indicates that such controls are effective. Although we have determined that the previously identified material weakness has been remediated as of December 31, 2019, we cannot assure you that we will not identify other material weaknesses or deficiencies, which could negatively impact our results of operations in future periods.

More generally, if we are unable to meet the demands that have been placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, we may be unable to accurately report our financial results in future periods, or report them within the timeframes required by law or stock exchange regulations. Failure to comply with the Sarbanes-Oxley Act, when and as applicable, could also potentially subject us to sanctions or investigations by the SEC or other regulatory authorities. Any failure to maintain or implement required new or improved controls, or any difficulties we encounter in their implementation, could result in additional material weaknesses or significant deficiencies, cause us to fail to meet our reporting obligations or result in material misstatements in our financial statements. Furthermore, if we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed, and investors could lose confidence in our reported financial information. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

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.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

In December 2017, President Trump signed into law the TCJA, which makes significant changes to the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation and other changes that may impact our operations, in particular the operations of our wholly-owned U.S. subsidiary, Orchard Therapeutics North America.

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

We operate through various subsidiaries in a number of countries throughout the world. Consequently, we are subject to tax laws, treaties, and regulations in the countries in which we operate, and these laws and treaties are subject to interpretation. We have taken, and will continue to take, tax positions based on our interpretation of such tax laws. Our transfer pricing arrangements are not generally binding on applicable tax authorities. The price charged for products, services, or the royalty rates and other amounts paid for intellectual property rights, could be challenged by the various tax authorities, resulting in additional tax liability, interest, and/or penalties. There can be no assurance that a taxing authority will not have a different interpretation of applicable law and assess us with additional taxes. If we are assessed with additional taxes, this may result in a material adverse effect on our results of operations and/or financial condition.

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 2019 taxable year, however, 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 (1) 75% or more of our gross income consists of passive income or (2) 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 shares, the U.S. holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

We do not believe that we were a PFIC in the 2019 taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by the spending of the cash we raise in any offering.

In certain circumstances, a U.S. holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a “qualified electing fund,” or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute “marketable” securities under the Code), which each require the inclusion of a pro rata share of our income on a current basis. However, a U.S. holder may make a QEF election with respect to our ordinary shares or ADSs only if we agree to furnish such U.S. holder annually with required information, and we have not determined if we intend to prepare or provide the information that would enable U.S. holders to make a QEF election. However, a U.S. holder would 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 U.K. net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable U.K. tax legislation.

As a U.K. incorporated and tax resident entity, we are subject to U.K. 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 U.K. corporation tax. As of December 31, 2019, we had cumulative carryforward tax losses of \$266.8 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 U.K. profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of U.K. 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 U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these tax credit cash rebate claims. Our eligibility to claim payable research and development tax credits may be limited or eliminated because we may no longer qualify as a small or medium-sized company. We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. 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, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change tax attributes (such as research 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 a change in control as defined by IRC Section 382. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we incur U.S. federal tax liability, our ability to use our pre-change tax attributes carryforwards to offset U.S. federal tax liability may be subject to limitations, which could potentially result in increased future tax liability to us.

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 can 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. The change to existing rules, future changes, if any, or the need for us to modify a current tax or accounting position may adversely affect our reported financial results or the way we conduct our business.

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 which 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 U.K. 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 depository bank.
- Under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise.
- Under English law and our Articles of Association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the Articles of Association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve other 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.
- The quorum requirement for a shareholders’ meeting is a minimum of two shareholders entitled to vote at the meeting and present in person or by proxy or, in the case of a shareholder which is a corporation, represented by a duly authorized officer. Under U.S. law, a majority of the shares eligible to vote must generally be present (in person or by proxy) at a shareholders’ meeting in order to constitute a quorum. The minimum number of shares required for a quorum can be reduced pursuant to a provision in a company’s certificate of incorporation or bylaws, but typically not below one-third of the shares entitled to vote at the meeting.

Item 1B. Unresolved Staff Comments.

There are no written comments from the staff of the U.S. Securities and Exchange Commission which remain unresolved before the end of the fiscal year to which this Annual Report relates.

Item 2. Properties.**Facilities**

Our principal office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom. We lease approximately 14,000 square feet of office space at this location and our lease for this location extends through January 2023.

We also lease approximately 14,000 square feet of office space in Boston, Massachusetts, and approximately 14,000 and 9,000 square feet of research and development laboratories and office space in Menlo Park, California.

In December 2018, we entered into an agreement to lease approximately 153,000 square feet of manufacturing and office space in Fremont, California to support our manufacturing expansion. This lease extends through May 2030. We expect to spend approximately \$84.5 million to fund the design and initial construction of this facility, including the necessary laboratory and manufacturing equipment, to support our long-term capacity needs for our product pipeline.

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, 2019, we were not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information and Holders of Ordinary Shares and ADSs

Our American Depositary Shares, or ADSs, each represent one ordinary share, nominal value £0.10 per share, of Orchard Therapeutics plc. An ADS may be evidenced by an American Depositary Receipt issued by Citibank, N.A. as depositary bank. Our ADSs have been listed and traded on The Nasdaq Global Select Market under the symbol “ORTX” since October 31, 2018. As of February 14, 2020, there were approximately 97,068,993 holders of record of our ordinary shares, nominal value £0.10 per share, and 97,068,993 holders of record of our ADSs. The closing sale price per ADS on The Nasdaq Global Select Market on February 14, 2020 was \$12.60.

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.

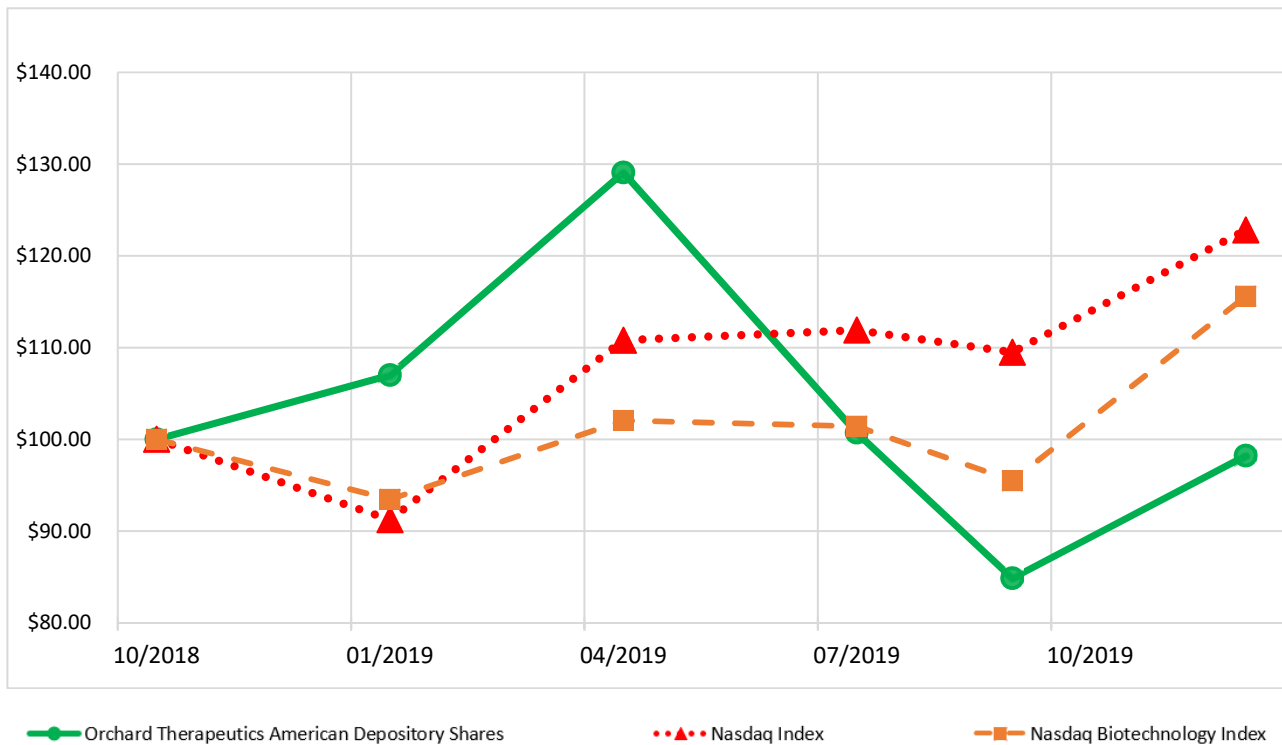
The payment of dividends by us is governed by English law. The declaration and payment of any future dividends will be at the discretion of our board of directors and will depend upon our results of operations, cash requirements, financial condition, contractual restrictions, restrictions imposed by 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.

Performance Graph

Set forth below is a graph comparing the total cumulative returns of Orchard Therapeutics plc, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes \$100 was invested on October 31, 2018 in our ADSs and each of the indices and that all dividends, if any, are reinvested. The performance shown represents past performance and should not be considered an indication of future performance.



This performance graph shall not be deemed “soliciting material” or to be “filed” with the U.S. Securities and Exchange Commission or subject to Regulation 14A or 14C, or to the liabilities of Section 18 of the Securities and Exchange Act of 1934, as amended, or the Exchange Act, except to the extent that we specifically request that this information be treated as soliciting material or we specifically incorporate it by reference into a filing under the Securities Act of 1933, as amended, or the Exchange Act.

Item 6. Selected Financial Data.

The following tables present the selected consolidated financial data as of the dates and for the periods indicated for Orchard Therapeutics plc. We derived the selected consolidated statements of operations and comprehensive loss data for the years ended December 31, 2019, 2018, and 2017 and the consolidated balance sheet data as of December 31, 2019 and 2018 from our audited consolidated financial statements included elsewhere in this Annual Report. The consolidated balance sheet data as of December 31, 2017 is derived from our consolidated financial statements not included in this Annual Report.

Our historical results are not necessarily indicative of our future results. This data should be read together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report.

Although we are a UK company, the functional currency of our reporting entity is the U.S. Dollar. Where the local currency of our subsidiaries is not U.S. dollars, our assets and liabilities are translated at the exchange rates at the balance sheet date, our revenue and expenses are translated at average exchange rates and shareholders’ equity is translated based on historical exchange rates. Translation adjustments are not included in determining net loss but are included in foreign exchange translation adjustment within accumulated other comprehensive loss, a component of shareholders’ equity.

Foreign currency transactions in currencies different from the functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recorded in other expense in the statement of operations and comprehensive loss.

As of December 31, 2019, the last business day of the fiscal year ended December 31, 2019, the representative exchange rate was £1.00 = \$1.3118.

| | Year Ended December 31, | | |
|---|-------------------------|--------------|-------------|
| | 2019 | 2018 | 2017 |
| (in thousands, except share and per share amounts) | | | |
| Consolidated Statement of Operations and Comprehensive Loss Data: | | | |
| Product Sales, net | \$ 2,513 | \$ 2,076 | \$ — |
| Costs and operating expenses: | | | |
| Cost of product sales | 805 | 422 | - |
| Research and development | 117,363 | 205,319 | 32,527 |
| Selling, general and administrative | 57,218 | 31,366 | 5,985 |
| Total operating expenses | 175,386 | 237,107 | 38,512 |
| Loss from operations | (172,873) | (235,031) | (38,512) |
| Other income (expense), net | 7,211 | 5,506 | (1,179) |
| Net loss before income taxes | (165,662) | (229,525) | (39,691) |
| Income tax benefit (expense) | 2,240 | (970) | (53) |
| Net loss attributable to ordinary shareholders | \$ (163,422) | \$ (230,495) | \$ (39,744) |
| Other comprehensive (loss) income: | (1,121) | (964) | 4,398 |
| Total comprehensive loss | \$ (164,543) | \$ (231,459) | \$ (35,346) |
| Net loss per share attributable to ordinary shareholders, basic and diluted | \$ (1.75) | \$ (10.22) | \$ (4.48) |
| Weighted average number of ordinary shares outstanding, basic and diluted | 93,240,355 | 22,559,389 | 8,872,768 |
| | As of December 31, | | |
| | 2019 | 2018 | 2017 |
| | (in thousands) | | |
| Consolidated Balance Sheet Data: | | | |
| Cash, cash equivalents, and marketable securities | \$ 324,990 | \$ 335,844 | \$ 89,856 |
| Working capital (1) | 294,040 | 307,612 | 83,466 |
| Total debt, net | 24,699 | — | — |
| Total assets | 399,281 | 366,042 | 97,294 |
| Total shareholders' equity | 299,193 | 311,338 | 86,405 |

(1) We define working capital as current assets less current liabilities.

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.

We have historically conducted our business through Orchard Therapeutics (Europe) Limited (formerly Orchard Therapeutics Limited) and subsidiaries. Following the completion of our initial public offering in November 2018, our consolidated financial statements present the consolidated results and operations of Orchard Therapeutics plc and subsidiaries.

Business Overview

Orchard Therapeutics is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous 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. The company has one of the deepest gene therapy product candidate pipelines in the industry and is advancing seven clinical-stage programs across multiple therapeutic areas, including inherited neurometabolic disorders, primary immune deficiencies and blood disorders, where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

Since our inception in 2015, we have devoted substantially all of our resources to conducting research and development of our product candidates, in-licensing and acquiring rights to our product candidates, business planning, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of equity securities, including ADSs and convertible preferred shares. Through December 31, 2019, we had received net proceeds of \$335.1 million from sales of ADSs in our initial public offering and follow-on public offering, \$283.4 million from sales of our convertible preferred shares, and \$24.5 million from our senior term facilities agreement (the “Credit Facility”) with MidCap Financial (Ireland) Limited (“MidCap Financial”).

We have incurred significant operating losses since our inception in 2015. With the exception of our commercial product Strimvelis[®], which was acquired in April 2018, we will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. Our net losses were \$163.4 million and \$230.5 million for the years ended December 31, 2019 and 2018, respectively. As of December 31, 2019, and 2018, we had an accumulated deficit of \$453.7 million and \$290.2 million, respectively. As of December 31, 2019, we had cash, cash equivalents, and marketable securities of \$325.0 million, excluding restricted cash. 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.

Components of our results of operations

Revenue

Since inception through December 31, 2019, we have generated \$4.6 million in net revenue from product sales for sales of Strimvelis. We do not expect to generate any significant revenue from the sale of products, with the exception of Strimvelis, in the near future. Our product candidate, OTL-200, for the treatment of MLD is currently under review with the European Medicines Agency and we expect a regulatory decision on approval in 2020. If that product candidate is approved and we are able to identify patients and secure reimbursement for our treatment, we will begin to generate revenue from the sale of such product candidate. If our development efforts for our other product candidates that we may develop in the future are successful and result in regulatory approval, or collaboration or license agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from collaboration or license agreements.

During the year ended December 31, 2019, we recognized \$2.5 million in net product sales. Strimvelis is currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. We expect that product sales of Strimvelis will fluctuate quarter over quarter, in particular as we continue to promote the product and increase market access. Net product sales for the year ended December 31, 2019 may not be representative of our sales for any future period.

Cost of product sales

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

Operating expenses

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts and the development of our product candidates, and include:

- expenses incurred under agreements with third parties, including CROs that conduct research, preclinical activities and clinical trials on our behalf as well as contract manufacturing organizations that manufacture lentiviral vectors and cell-based drug products for use in our preclinical and clinical trials;
- expenses to acquire technologies to be used in research and development;
- salaries, benefits and other related costs, including share-based compensation expense, for personnel engaged in research and development functions;
- costs of outside consultants, including their fees, share-based compensation and related travel expenses;
- the costs of laboratory supplies and acquiring, developing and manufacturing preclinical study and clinical trial materials;
- costs related to compliance with regulatory requirements;
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities 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 cost 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 a prepaid expense 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 (See Note 2 of our consolidated financial statements).

In 2018 we issued ordinary shares to various academic and health care institutions as part of the consideration for entering into several license agreements to in-license intellectual property rights and know-how relevant to our programs. This consideration was accounted for as research and development expense based on the fair value of the shares issued as of the time the agreements were executed or amended.

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and contract manufacturing organizations in connection with our preclinical and clinical development activities. License fees and other costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. License fees and other costs incurred prior to designating a product candidate for development are included in other program expense. We do not allocate employee costs, costs associated with our 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 increase for the foreseeable future as a result of our expanded portfolio of product candidates and as we: (i) expedite the clinical development and seek to obtain marketing approval for our lead product candidates, including OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS; (ii) initiate additional clinical trials for our product candidates, including OTL-102 for X-CGD, OTL-300 for TDT, OTL-201 for MPS-III A, and OTL-203 for MPS-I; (iii) seek to improve the efficiency and scalability of our manufacturing processes and supply chain; and (iv) build our in-house process development, analytical and manufacturing capabilities and continue to discover and develop additional product candidates. We also expect to incur additional expenses related to milestone, royalty payments and maintenance fees payable to third parties with whom we have entered into license agreements to acquire the rights related to our product candidates.

The successful development of our product candidates and commercialization of Strimvelis and our product candidates, if approved, is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the following:

- completing research and preclinical development of our product candidates and identifying new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing 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 regulatory compliance for Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and private payors for 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 Strimvelis and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and compliance systems;
- 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.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA, EMA or another regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant trial delays due

to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development and we may never succeed in obtaining regulatory approval for any of our product candidates.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, commercial, corporate and business development, and administrative functions. Selling, general and administrative expenses also include professional fees for legal, patent, accounting, auditing, tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

We expect that our selling, general and administrative expenses will increase in the future as we increase our selling, general and administrative headcount to support our continued research and development and potential commercialization of our expanded portfolio of product candidates. In addition, we are expanding our organization into multiple countries in Europe to support the potential commercialization of OTL-200 for MLD, which is currently under regulatory review by the EMA. We also expect to incur increased expenses associated with compliance with our obligations as a public company, including costs of accounting, audit, legal, regulatory and tax compliance services, director and officer insurance costs and investor and public relations 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. The Credit Facility bears a variable interest rate at a rate of 6.0% above LIBOR, plus a final payment equal to 4.5% of the principal borrowed under the Credit Facility. In fiscal year 2020, we will have a full year of interest expense, as compared to 7 months in 2019.

Other income (expense)

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

Results of operations

Information pertaining to fiscal year 2017 was included in the Company's Annual Report on Form 20-F for the year ended December 31, 2018 on page 122 under Item 5, "Operating and Financial Review and Prospects," which was filed with the U.S. Securities and Exchange Commission on March 22, 2019

Comparison of the years ended December 31, 2019 and 2018

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018:

| | Year Ended December 31, | | Change |
|--|-------------------------|--------------|-----------|
| | 2019 | 2018 | |
| | (in thousands) | | |
| Product sales, net | \$ 2,513 | \$ 2,076 | \$ 437 |
| Cost and operating expenses: | | | |
| Cost of product sales | 805 | 422 | 383 |
| Research and development | 117,363 | 205,319 | (87,956) |
| Selling, general and administrative | 57,218 | 31,366 | 25,852 |
| Total operating expenses | 175,386 | 237,107 | (61,721) |
| Loss from operations | (172,873) | (235,031) | 62,158 |
| Other income (expense): | | | |
| Interest income | 7,362 | 1,116 | 6,246 |
| Interest expense | (1,538) | — | (1,538) |
| Other income (expense), net | 1,387 | 4,390 | (3,003) |
| Total other income (expense) | 7,211 | 5,506 | 1,705 |
| Net loss before income tax | (165,662) | (229,525) | 63,863 |
| Income tax benefit (expense) | 2,240 | (970) | 3,210 |
| Net loss attributable to ordinary shareholders | \$ (163,422) | \$ (230,495) | \$ 67,074 |

Research and development expenses

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

| | Year ended December 31 | | Change |
|---|------------------------|------------|-------------|
| | 2019 | 2018 | |
| | (in thousands) | | |
| Direct research and development expenses by therapeutic area: | | | |
| Neurometabolic disorders | \$ 39,042 | \$ 87,243 | (48,201) |
| Primary immune deficiencies | 28,775 | 101,234 | (72,459) |
| Blood disorders | 3,988 | 2,468 | 1,520 |
| Other research and preclinical programs under development | 737 | 15 | 722 |
| Research and discovery and unallocated costs | | | |
| Personnel related (excluding share-based compensation) | 31,004 | 18,852 | 12,152 |
| Share-based compensation | 7,425 | 2,740 | 4,685 |
| Accretion of Strimvelis loss provision | (3,833) | (6,301) | 2,468 |
| Research and development tax credit | (17,564) | (10,213) | (7,351) |
| Facility and other | 27,789 | 9,281 | 18,508 |
| Total research and development expenses | \$ 117,363 | \$ 205,319 | \$ (87,956) |

The overall decline in research and development expenses of \$88.0 million is due to the absence of a \$133.6 million in-process research and development charge associated with the GSK transaction in 2018. This charge in 2018 was primarily allocated to programs within the neurometabolic disorders and the primary immune deficiencies therapeutic areas. The charge was partially offset by increases in spending on programs and unallocated costs, as described below.

Direct research and development expenses for neurometabolic programs declined by \$48.2 million. The decline is primarily driven by a \$69.3 million in-process research and development charge for OTL-200 related to the GSK transaction that occurred in 2018. Excluding the effects of this charge, direct expenses associated with OTL-200 increased by \$3.0 million compared to 2018. In addition, we incurred an increase in spending of \$17.2 million on our OTL-203 for MPS-I, which primarily relates to the upfront and clinical milestone expenses incurred upon entering into our license arrangement with Telethon-OSR in May 2019. Direct expenses for OTL-201 increased by \$0.3 million compared to 2018, which was primarily attributable to increases in manufacturing and process development-related costs.

Direct research and development expenses for primary immune deficiency-related programs declined by \$72.5 million. The decline is primarily driven by a \$64.3 million in-process research and development charge for OTL-103 related to the GSK transaction that occurred in 2018. Excluding the effects of this charge, direct expenses associated with OTL-103 increased by \$1.1 million compared to 2018. Direct expenses associated with OTL-101 declined by \$5.3 million, due to a \$7.0 million decrease in manufacturing and process development costs with third-party contract manufacturers compared to 2018. Direct expenses for Strimvelis also declined by \$2.9 million due to a decline in research and development-related manufacturing costs, and costs associated with transitioning of Strimvelis from GSK that were incurred in 2018, but did not recur in 2019.

Direct research and development expenses for blood disorder-related programs increased by \$1.5 million in 2019 due to increased expenses for OTL-300 compared to 2018. The increase in costs related to OTL-300 was primarily due to increased clinical trial costs. The increase in costs associated with other research and preclinical programs relates to costs associated with having additional early-stage programs in our pipeline in 2019 compared to 2018.

Unallocated research and development costs and offsets to research and development expenses increased by \$30.3 million generally due to an increase in personnel related costs of \$12.2 million and share-based compensation of \$4.7 million. Further, other research and development costs such as lab supplies and consumables, external manufacturing and process development, and other unallocated costs not yet attributable to a specific developmental program increased by \$13.7 million in 2019 compared to 2018. Occupancy costs increased by \$4.5 million, generally associated with a full year of lease expense associated with our Fremont manufacturing facility. The increases noted above were offset by an increase in the U.K. research and development tax credit that is recorded as an offset to research and development expense of \$7.3 million. Amortization of the Strimvelis loss provision, which is also accounted for as an offset to research and development expense, declined by \$2.5 million in 2019, attributable to lower costs incurred for our Strimvelis program compared to 2018.

Selling, general and administrative expenses

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

| | Year ended December 31 | | Change |
|---|------------------------|------------------|------------------|
| | 2019 | 2018 | |
| | (in thousands) | | |
| Selling, general and administrative expenses: | | | |
| Personnel (excluding share-based compensation) | \$ 18,864 | \$ 9,586 | 9,278 |
| Share-based compensation | 11,999 | 4,026 | 7,973 |
| Consulting, professional, and insurance-related costs | 11,077 | 7,660 | 3,417 |
| Marketing and promotions | 8,060 | 1,991 | 6,069 |
| Facilities and IT-related costs | 3,161 | 2,972 | 189 |
| Other | 4,057 | 5,131 | (1,074) |
| Total selling, general, and administrative expenses: | <u>\$ 57,218</u> | <u>\$ 31,366</u> | <u>\$ 25,852</u> |

Selling, general and administrative expenses were \$57.2 million in 2019, compared to \$31.4 million in 2018. The increase of \$25.9 million was primarily due to increased personnel-related costs of \$9.3 million from an increased headcount in our selling, general and administrative functions. Share-based compensation expense increased by \$8.0 million in 2019 compared to 2018 due to the higher number of employees receiving grants. Consulting, professional, and insurance-related costs increased by \$3.4 million, primarily due to a \$2.0 million increase in directors and officers insurance as a result of being a public company for a full year in 2019. Expenses associated with marketing and commercialization of Strimvelis, and costs associated with preparing for the potential future commercialization of our product candidates, if approved, increased by \$6.1 million.

Other income (expense), net

Other income, net for 2019 and 2018 was \$7.2 million and \$5.5 million, respectively. During 2019, we had realized and unrealized gains on foreign currency transactions of \$1.4 million, compared to \$4.4 million for 2018. Additionally, we had interest income of \$7.3 million in 2019, compared to \$1.1 million in 2018. The increase in interest income of \$6.2 million relates to interest from our cash equivalents and marketable securities after investing the proceeds received from our initial public offering and follow-on offering. The increase in interest expense of \$1.5 million in 2019 is attributable to our Credit Facility, which we entered into in May 2019 and was therefore not in place in 2018.

Liquidity and capital resources.

From our inception through December 31, 2019, we have generated \$4.6 million from product sales and incurred significant operating losses and negative cash flows from our operations. We currently have only one commercial product, Strimvelis, which we acquired from GSK in April 2018 and our product candidates are in various phases of preclinical and clinical development. OTL-200 is currently under regulatory review by the European Medicines Agency and we expect a decision in 2020. We do not expect to generate significant revenue from sales of any products in 2020 and until we have obtained additional regulatory approvals, secured broader reimbursement and gained product acceptance. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our initial public offering and follow-on offering, proceeds from the sale of convertible preferred shares, 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 CIRM, and our Credit Facility.

Through December 31, 2019, we have received net proceeds of \$335.2 million from the sale of ADSs in our initial public offering and follow-on offering, net proceeds of \$283.4 million from sales of convertible preferred shares, \$24.5 million in net proceeds from our Credit Facility, and reimbursement of \$7.9 million from our agreement with CIRM, which was formerly a subcontract agreement with UCLA. As of December 31, 2019, we had cash, cash equivalents, and marketable securities of \$325.0 million, excluding restricted cash.

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

Cash flows

Information pertaining to fiscal year 2017 was included in the Company's Annual Report on Form 20-F for the year ended December 31, 2018 on page 122 under Item 5, "Operating and Financial Review and Prospects," which was filed with the U.S. Securities and Exchange Commission on March 22, 2019.

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

| | Year Ended December 31, | |
|---|-------------------------|-------------------|
| | 2019 | 2018 |
| | (in thousands) | |
| Net cash used in operating activities | \$ (166,131) | \$ (97,536) |
| Net cash used in investing activities | (309,358) | (4,032) |
| Net cash provided by financing activities | 157,453 | 354,864 |
| Effect of exchange rate changes on cash | 1,672 | (3,471) |
| Net increase in cash, cash equivalents, and restricted cash | <u>\$ (316,364)</u> | <u>\$ 249,825</u> |

Operating activities

During 2019, operating activities used \$166.1 million of cash, primarily resulting from our net loss of \$163.4 million. Cash usage from changes in our operating assets and liabilities was \$17.7 million, which was primarily driven by an increase in our research and development tax credit receivable of \$17.6 million. Non-cash adjustments to operating activities of \$15.0 million was generally due to \$19.4 million in non-cash share-based compensation expense, offset by \$3.9 million in amortization of the Strimvelis loss provision as an offset to research and development expense. Further, there were unrealized foreign currency transaction gains on investments held by our U.K. subsidiary of \$1.9 million. Included within operating activities was a cash payment of \$17.2 million for our upfront and milestone payments associated with entering into our MPS-I license agreement with Telethon-OSR.

During 2018, operating activities used \$97.5 million of cash, primarily resulting from our net loss of \$230.5 million, off-set by net cash provided by changes in our operating assets and liabilities of \$36.5 million and net non-cash charges and credits of \$96.5 million, which included \$93.4 million for the issuance of our preferred shares as non-cash license fees under the GSK Agreement, \$6.8 million in non-cash share-based compensation, \$1.4 million in non-cash milestone expense, and \$1.2 million in depreciation expense. These amounts were offset by a \$6.3 million reduction in the Strimvelis loss provision. Net cash provided by changes in our operating assets and liabilities for 2018 is primarily due to the impact of a \$10.1 million increase in our research and development tax credit receivable and a \$6.8 million increase in other receivables, prepaid expenses and other assets, offset by a \$31.7 million increase in accrued expenses and other current liabilities, a \$6.9 million increase in other long-term liabilities, and a \$14.8 million increase in accounts payable. Included within operating activities was a cash payment of \$14.2 million for the GSK upfront license fee.

The change in net cash used in operating activities from 2018 to 2019 is the result of our increased net loss, excluding the non-cash in-process research and development charge of \$93.4 million from the GSK agreement which was settled with preferred shares, and generally due to growth in our business and the advancement of our development programs, as described in “—Results of operations.”

Investing activities

During 2019, 2018, and 2017, we used \$309.4 million, \$4.0 million and, \$1.6 million, respectively, of cash in investing activities. The increase in cash used for investing activities in 2019 compared to prior years is attributable to the investing of the proceeds received from our initial public offering, follow-on offering, and term loan for the purchase of \$414.0 million of highly-rated, short duration marketable securities, offset by the sale and maturity of such securities of \$109.0 million. We expect the cash used in investing activities for capital expenditures to increase substantially in the future to fund the construction and equipment to build-out our manufacturing facility in Fremont, California.

Financing activities

During 2019, we had proceeds from our follow-on offering of \$129.7 million, net of underwriting discounts and issuance costs paid, and proceeds from the issuance of our term loan of \$24.5 million, net of debt issuance costs. Additionally, we had proceeds of \$3.3 million from the exercise of share options and issuance of ordinary shares as part of our 2018 Employee Stock Purchase Plan, or ESPP.

During 2018, net cash provided by financing activities was \$354.9 million, consisting of \$2.3 million of net proceeds from subsequent closing of our Series B convertible preferred shares in January 2018, \$147.1 million of net proceeds from the sale of our Series C convertible preferred shares in August 2018, and \$205.5 million of net proceeds from the sale of our ADSs in our initial public offering in November 2018.

Funding requirements

We expect our expenses and capital expenditures to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates and as we:

- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of Strimvelis in the European Union, and 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;
- conduct IND and CTA-enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates;
- seek to identify and develop, acquire or in-license additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe our existing cash, will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2021. 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 U.K. research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure Credit ("RDEC") program depending on eligibility. 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, 2019, 2018 and 2017.

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 U.K. government which are subject to interpretation. At each period end, we estimate the reimbursement available to us based on available information at the time.

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

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The

majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our prepaid and accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time.

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

Valuation of share-based compensation

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

The fair value of each share option is estimated on the date of grant using the Black-Scholes option pricing model. Until the completion of our initial public offering in November 2018, we had been a private company and lacked company-specific historical and implied volatility information for our shares. Therefore, we estimate our expected share price volatility based on the historical volatility of publicly traded peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded share price. The expected term of our share options has been determined utilizing the “simplified method” for awards that qualify as “plain-vanilla” options. Prior to the adoption of ASU 2018-07, the expected term of share options granted to non-employees was the contractual term. After adoption of ASU 2018-07, the expected term of share options granted to non-employees is determined in the same manner as share options granted to employees. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends on our ordinary shares and do not expect to pay any cash dividends in the foreseeable future.

Off-balance sheet arrangements.

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Tabular disclosure of contractual obligations.

The following table summarizes our contractual obligations as of December 31, 2019 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods:

| | Total | Payments Due By Period | | | |
|---------------------------------|-----------|------------------------|-----------------|-----------------|----------------------|
| | | Less Than 1 Year | 1 to 3 Years | 4 to 5 Years | More Than 5 Years |
| | | | | | |
| | | (in thousands) | | | |
| Manufacturing commitments (1) | \$ 10,146 | \$ 5,586 | \$ 4,560 | \$ — | \$ — |
| Operating lease commitments (2) | \$ 43,120 | \$ 6,498 | \$ 10,422 | \$ 7,329 | \$ 18,871 |
| Debt commitments (3) | \$ 30,607 | \$ 1,955 | \$ 16,234 | \$ 12,418 | \$ — |
| Total | \$ 83,873 | \$ 14,039 | \$ 31,216 | \$ 19,747 | \$ 18,871 |

- (1) Amounts reflect commitments for costs associated with our external contract manufacturing organizations, which we engaged to manufacture clinical trial materials. Our manufacturing commitment included non-cancelable minimum payments to be made as of December 31, 2019.

- (2) Amounts reflect minimum payments due for our office and laboratory space leases. Further information about our leases is described in Note 7 of our consolidated financial statements.
- (3) Amounts in the table reflect contractually required principal, interest, and final payments payable under the Credit Facility. For the purposes of this table, the interest due under the Credit Facility was calculated using an assumed interest rate of 7.7% per annum, which was the interest rate in effect as of December 31, 2019. The table also assumes repayment of the term loan beginning 24 months following the date of the Credit Facility.

We enter into contracts in the normal course of business with contract manufacturing organizations and other third parties for clinical trials and preclinical research studies and testing. Manufacturing commitments in the preceding table include agreements that are enforceable and legally binding on us and that specify all significant terms, including fixed or minimum quantities to be purchased, fixed, minimum or variable price provisions, and the approximate timing of the transaction. For obligations with cancellation provisions, the amounts included in the preceding table are limited to the non-cancelable portion of the agreement terms or the minimum cancellation fee.

Excluding our agreement with GSK, we may incur potential contingent payments totaling up to \$68.0 million upon our achievement of clinical, regulatory and commercial milestones, as applicable, or royalty payments that we may be required to make under license agreements we have entered into with various entities pursuant to which we have in-licensed certain intellectual property. Pursuant to our agreement with Oxford BioMedica, we may incur the obligation to issue additional ordinary shares upon the achievement of a certain development milestone. Due to the uncertainty of the achievement and timing of the events requiring payment under these agreements, the amounts to be paid by us are not fixed or determinable at this time and are excluded from the table above.

In January 2018, we leased office space in London, United Kingdom, with a term through January 2023. The annual rent commitment is approximately \$0.8 million. In November 2017, we leased office and laboratory space in Menlo Park, California with a term through December 2020. The annual rent commitment is approximately \$0.8 million. In March 2018, we leased office space in Boston, Massachusetts, with a term through September 2022. The annual rent commitment is approximately \$0.3 million. In December 2018, we leased office and manufacturing space in Fremont, California, with a term through May 2030. The annual rent commitment is approximately \$2.8 million. In December 2018, we leased additional office space in London, United Kingdom, with a term through January 2023. The annual rent commitment is approximately \$0.1 million. Finally, in January 2020, we commenced a lease in Boston, Massachusetts for office space with a term through September 2026. The annual rent commitment is approximately \$0.8 million.

Under the GSK Agreement, we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired by GSK and OTL-101. We will pay a mid-single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digit to the low teens for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. We may pay up to an aggregate of £90.0 million in milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048.

As consideration for the licenses and options in the Telethon-OSR agreements acquired and assumed in the GSK Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are also required to pay Telethon-OSR a fee in connection with the exercise of our option for each collaboration program. We are obligated to pay up to an aggregate of €31.0 million in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDBT programs). Additionally, we are 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 sublicensees of the collaboration programs. In May 2019, we 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 hematopoietic stem cell lentiviral based gene therapy for the treatment of MPS-I, including the Hurler variant. Under the terms of the agreement, Telethon-OSR is entitled to receive €15 million combined upfront and milestone payment from us. We are also 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.

In May 2019, we entered into a Credit Facility with MidCap Financial, as agent, and additional lenders from time to time (together with MidCap Financial, the “Lenders”), to borrow up to \$75.0 million in term loans. To date, we have borrowed \$25.0 million under an initial term loan. The remaining \$50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a \$25.0 million term loan available no earlier than September 30, 2019 and no later than December 31, 2020 upon submission of certain regulatory filings and evidence of our having \$100 million in cash and cash equivalent investments; and the third term loan being a \$25.0 million term loan available no earlier than July 1, 2020 and no later than September 30, 2021 upon certain regulatory approvals and evidence of the Company having \$125 million in cash and cash equivalent investments. Each term loan under the Credit Facility bears interest at an annual rate equal to 6% plus LIBOR. We are required to make interest-only payments on the term loan for all payment dates prior to 24 months following the date of the Credit Facility, unless the third tranche is drawn, in which case the Company is required to make interest-only payments for all payment dates prior to 36 months following the date of the Credit Facility. The term loans under the Credit Facility will begin amortizing on either the 24-month or the 36-month anniversary of the Credit Facility (as applicable), with equal monthly payments of principal plus interest to be made by us to the Lenders in consecutive monthly installments until the loan matures. In addition, a final payment of 4.5% is due on maturity. We are currently eligible to draw down the second term loan totaling \$25.0 million following the recent regulatory filing with the European Medicines Agency for OTL-200 for MLD.

It is expected that LIBOR will be phased out by the end of 2021. The Alternative Reference Rates Committee of the Federal Reserve Board has identified the Secured Overnight Financing Rate (SOFR) as the preferred alternative to LIBOR. As our Credit Facility utilizes LIBOR as a factor in determining the applicable interest rate, the expected discontinuation and transition may require us to renegotiate certain terms of the agreement to replace LIBOR with a new reference rate, which could increase the cost of servicing our debt and have an adverse effect on our results of operations and cash flows.

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

Interest rate sensitivity

As of December 31, 2019, we had cash, cash equivalents, marketable securities, and restricted cash of \$329.2 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, US treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We have borrowed \$25.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 6% plus LIBOR. As of December 31, 2019, the carrying value of the term loans under the credit facility was \$24.7 million.

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 a foreign currency gain of \$1.5 million \$4.4 million and a \$1.2 million loss for the years ended December 31, 2019, 2018 and 2017, respectively. 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 income (loss) but are included in our foreign exchange 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

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2019. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to provide reasonable assurance that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to provide reasonable assurance that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. 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. Based on the evaluation of our disclosure controls and procedures as of December 31, 2019, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Remediation of Previously Reported Material Weakness

Our management previously identified deficiencies that were concluded to represent a material weakness in our internal control over financial reporting where we did not design or implement sufficient controls and other review procedures performed by personnel familiar with U.S. GAAP to evaluate the recognition and accrual of research and development related expenses and reimbursements. A material weakness is defined as a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected and corrected on a timely basis.

In response to the material weakness, we have enhanced our controls around the recognition and accrual of research and development related expenses and reimbursements, including:

- Hiring a third-party professional accounting consulting firm to assist in establishing and implementing appropriate financial reporting policies, processes and controls over the recognition and accrual of research and development related expenses and reimbursements;
- Documenting the step-by-step processes and controls necessary to ensure that the recognition and accrual of research and development related expenses and reimbursements are accounted for in accordance with U.S. GAAP;
- Enhancing documentation and controls supporting the recognition and accrual of research and development related expense and reimbursements; and
- Providing increased oversight and review of the accrual of research and development related expense and reimbursements by personnel familiar with U.S. GAAP.

These controls around our oversight and review of the accrual of research and development related expenses and reimbursements have operated for a sufficient period of time, and management's evaluation of such controls indicates that such controls are effective. We have determined that the previously identified material weakness has been remediated as of December 31, 2019.

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, 2019.

The effectiveness of our internal control over financial reporting as of December 31, 2019 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

During the year ended December 31, 2019, there was a change in our internal control over financial reporting (as defined in Rules 13a-16(f) and 15d-15(f) under the Exchange Act) as we designed and implemented controls to remediate the material weakness related to the recognition and accrual of research and development related expenses and reimbursements.

Item 9B. Other Information.

The following summary contains a description of material U.S. federal income tax and U.K. 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:

- An individual who is a citizen or individual resident of the United States;
- 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;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

PFIC Rules

If we are classified as a PFIC in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or

- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

We do not believe that we were a PFIC in the 2019 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a “controlled foreign corporation” for any taxable year (see discussion below in “Controlled foreign corporation considerations”), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future.

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

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

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

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

If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF Election. In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly

carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

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

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

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

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

WE STRONGLY URGE INVESTORS TO CONSULT YOUR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO YOUR INVESTMENT IN THE 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 2019 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 U.K. 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.

U.K. Taxation

The following is intended as a general guide to current U.K. tax law and HMRC published practice 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 U.K. 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 U.K. taxation. It is written on the basis that the company is and remains solely resident in the U.K. for tax purposes and will therefore be subject to the U.K. 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-U.K. 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 U.K. 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 U.K. 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 U.K. 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 U.K. direct tax purposes.

This guide may not relate to certain classes of U.K. 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 U.K. taxation on a remittance basis.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. 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-U.K. RESIDENT OR DOMICILED PERSONS 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 U.K. tax.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. 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 U.K. 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 U.K. through a permanent establishment, branch or agency to which the ADSs are attributable.

Dividend income is treated as the top slice of the total income chargeable to U.K. income tax. An individual U.K. Holder who receives a dividend in the 2019/2020 tax year will be entitled to a tax-free allowance of £2,000. Dividend income in excess of this tax-free allowance will be charged at 7.5% for basic rate taxpayers, 32.5% for higher rate taxpayers, and 38.1% for additional rate taxpayers.

Corporation tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. 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 U.K. Holders should not be subject to U.K. 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. If the conditions for the exemption are not satisfied, or such U.K. Holder elects for an otherwise exempt dividend to be taxable, U.K. corporation tax will be chargeable on the amount of any dividends (at the current rate of 19%).

Chargeable gains

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

If an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate is liable to U.K. capital gains tax on the disposal of ADSs, the applicable rate will be 20% (2019/2020). For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and liable to U.K. capital gains tax on such disposal, the applicable rate would be 10% (2019/2020), save to the extent that any capital gains exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (2019/2020).

If a corporate U.K. Holder becomes liable to U.K. corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of U.K. corporation tax (currently 19%) would apply.

A holder of ADSs which is not resident for tax purposes in the U.K. should not normally be liable to U.K. 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 in the United Kingdom through a permanent establishment, branch or agency to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the U.K. for a period of less than five years and who disposes of ADSs during that period may be liable on his or her return to the U.K. to U.K. 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 U.K. stamp duty or stamp duty reserve tax (or SDRT) is payable on the issue of underlying ordinary shares in the company.

Special rules apply where ordinary shares are issued or transferred to, or to a nominee or agent for, either a person whose business is or includes issuing depositary receipts or clearance services, under which stamp duty or SDRT may be charged at a higher rate of 1.5%, unless (in the case of a clearance service) the clearance service has made and maintained an election under section 97A of the U.K. 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 DTC.

However, based on current published practice following recent case law in respect of the European Council Directives 69/335/EEC and 2009/7/EC, or the Capital Duties Directives, HMRC has confirmed that it will not seek to impose stamp duty or SDRT at the rate of 1.5% on issues of UK shares to depositary receipt issuers or clearance services, or on transfers of such shares to such issuers or clearance services where those issues are integral to the raising of capital by a company. However, HMRC's view is that the relevant case law does not have any impact upon the transfer (on sale or otherwise than on sale) of shares or securities to depositary receipt systems or clearance services that are not an integral part of an issue of share capital and so the 1.5% SDRT or stamp duty charge will continue to apply to such transfers and therefore if ordinary shares are withdrawn from a depositary receipt system or clearance service, a charge to stamp duty or SDRT at 1.5% may arise on a subsequent redeposit of ordinary shares into any such system or clearance service.

It should also be noted that the 1.5% charge for all issues of shares into depositary receipt systems and clearance services remains as a provision of UK statute and that the removal of the 1.5% charge is based upon the provisions of EU law. There is therefore a risk that this could be affected by the UK's decision to leave the European Union and the expiry of any related transitional or implementation period (currently anticipated to be on 31 December 2020). The 2017 Autumn Budget included a statement that the government will not reintroduce the 1.5% charge on the issue of shares (and transfers integral to capital raising) into clearance services following the UK's exit from the EU, but the charge will remain as a provision of UK statute. To the extent that UK law is changed, or that the government's stated intention is changed, including as a result of the UK's decision to leave the European Union and/or the end of any transitional period, it is possible that the 1.5% charge may apply in respect of subsequent issues of ordinary shares to depositary receipt systems or clearance services (including where our ADSs are issued in respect of such underlying ordinary shares). Any stamp duty or SDRT payable on an issue of ordinary shares to a depositary receipt system or clearance service will in practice generally be paid by the participants in the clearance service or depositary receipt system. Specific professional advice should be sought before incurring a 1.5% stamp duty or SDRT charge in any circumstances.

Transfers of Ordinary Shares

An unconditional agreement to transfer ordinary shares will normally give rise to a charge to SDRT at the rate of 0.5% of the amount or value of the consideration payable for the transfer. The purchaser of the shares is liable for the SDRT. Transfers of ordinary shares in certificated form are generally also subject to stamp duty at the rate of 0.5% of the amount or value of the consideration given for the transfer (rounded up to the next £5.00). Stamp duty is normally paid by the purchaser. The charge to SDRT will be cancelled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

An unconditional agreement to transfer ordinary shares to, or 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, 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 U.K. 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 recent 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 where the transfer of ordinary shares to a clearance service or depositary receipt system outside the European Union is an integral part of an issue of share capital (although the relevant judgment refers to transfers which are integral to the raising of capital). In addition, a recent Court of Justice of the European Union judgment (*Air Berlin plc v HMRC* (2017)) held on the relevant facts that the Capital Duties Directives preclude the taxation of a transfer of legal title to shares for the sole purpose of listing those shares on a stock exchange which does not impact the beneficial ownership of the shares, but, as yet, the U.K. domestic law and HMRC's published practice remain unchanged and, accordingly, we anticipate that amounts on account of SDRT will continue to be collected by the depositary receipt issuer or clearance service.

It should also be noted that the 1.5% charge for all transfers of shares into depositary receipt systems and clearance services remains as a provision of UK statute and that the removal of the 1.5% charge in the case of transfers integral to the raising of capital is based upon the provisions of EU law. There is therefore a risk that this could be affected by the UK's decision to leave the European Union and the expiry of any related transitional or implementation period (currently anticipated to be on 31 December 2020). The 2017 Autumn Budget included a statement that the government will not reintroduce the 1.5% charge on the issue of shares (and transfers integral to capital raising) into clearance services following the UK's exit from the EU, but the charge will remain as a provision of UK statute. To the extent that UK law is changed, or that the government's stated intention is changed, including as a result of the UK's decision to leave the European Union and/or the end of any transitional period, it is possible that the 1.5% charge may apply in respect of subsequent transfers of ordinary shares to depositary receipt systems or clearance services even where such transfers are integral to the raising of capital.

Holders of ordinary shares should consult their own independent professional advisers before incurring or reimbursing the costs of any 1.5% SDRT charge. 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 participants in the clearance service or depositary receipt system.

Transfers of ADSs

No U.K. stamp duty will in practice be payable on a written instrument transferring an ADS provided that the instrument of transfer is executed and remains at all times outside the United Kingdom. Where these conditions are not met, the transfer of, or agreement to transfer, an ADS could, depending on the circumstances, attract a charge to U.K. stamp duty at the rate of 0.5% of the value of the consideration.

No SDRT will be payable in respect of an agreement to transfer an ADS.

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 2020 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 2020 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 2020 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 2020 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 2020 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:

| <u>Reports of Independent Registered Public Accounting Firms</u> | <u>Page</u> |
|---|-----------------|
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| | defined. |
| <u>Consolidated Balance Sheets</u> | F-2 |
| <u>Consolidated Statements of Operations and Comprehensive Loss</u> | F-3 |
| <u>Consolidated Statements of Convertible Preferred Shares and Shareholders' Equity</u> | F-4 |
| <u>Consolidated Statements of Cash Flows</u> | F-5 |
| <u>Notes to Consolidated Financial Statements</u> | F-6 |

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

None.

(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

| <u>Exhibit Number</u> | <u>Description</u> | <u>Incorporated by Reference herein from Form or Schedule</u> | <u>Exhibit</u> | <u>File Date</u> | <u>File Number</u> |
|-----------------------|---|---|----------------|------------------|--------------------|
| 2.1† | <u>Asset Purchase and License Agreement, by and among the registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Ltd., dated April 11, 2018 (Schedules, exhibits, and similar supporting attachments are omitted pursuant to Item 601(b)(2) of Regulation S-K. The registrant agrees to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request).</u> | Form F-1 | 2.1 | Oct. 4, 2018 | 333-227698 |
| 3.1 | <u>Articles of Association of Orchard Therapeutics plc</u> | Form 20-F | 1.1 | Mar. 22, 2019 | 001-38722 |
| 4.1 | <u>Deposit Agreement</u> | Form 20-F | 2.1 | Mar. 22, 2019 | 001-38722 |
| 4.2 | <u>Form of American Depositary Receipt (included in Exhibit 4.1)</u> | Form 20-F | 2.2 | Mar. 22, 2019 | 001-38722 |
| 4.3 | <u>Investment and shareholders' agreement by and between the registrant and the shareholders named therein, dated August 2, 2018, as amended.</u> | Form F-1 | 10.1 | Jun. 3, 2019 | 333-231916 |

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|---------|---|-------------|-------|---------------|------------|
| 4.4* | Description of the registrant's securities. | | | | |
| 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# | 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 |
| 10.5 | Director Nomination Agreement, dated as of October 18, 2018, by and between the registrant and Glaxo Group Limited. | Form F-1/A | 10.11 | Oct. 23, 2018 | 333-227698 |
| 10.6 | Deed of Novation, by and among the registrant, Glaxo Group Limited, GlaxoSmithKline Intellectual Property Development Limited, GlaxoSmithKline S.p.A., Fondazione Telethon and Ospedale San Raffaele (in its own capacity and as successor in interest to Fondazione Centro San Raffaele Del Monte Tabor), dated April 5, 2018. | Form F-1 | 10.4 | Oct. 4, 2018 | 333-227698 |
| 10.7 | Research and Development Collaboration and License Agreement, by and among Glaxo Group Limited, Fondazione Telethon and Fondazione Centro San Raffaele del Monte Tabor, dated October 15, 2010, as amended. | Form F-1 | 10.5 | Oct. 4, 2018 | 333-227698 |
| 10.8 | Lease Agreement, dated as of January 19, 2018, by and between the Registrant and New Connect Investments Limited. | Form F-1 | 10.7 | Oct. 4, 2018 | 333-227698 |
| 10.9†† | Lease Agreement, dated as of December 11, 2018, by and between BPP Pacific Industrial CA Non-REIT Owner 2 LLC and Orchard Therapeutics North America. | Form 20-F/A | 4.12 | Apr. 26, 2019 | 001-38722 |
| 10.10† | License and Development Agreement, by and between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016, as amended. | Form F-1 | 10.8 | Oct. 4, 2018 | 333-227698 |
| 10.11† | License Agreement between UCL Business Plc, The Regents of the University of California and the registrant, dated February 6, 2016, as amended. | Form F-1 | 10.9 | Oct. 4, 2018 | 333-227698 |
| 10.12 | Senior Term Facilities Agreement by and among the registrant, as borrower and guarantor, the other guarantors from time to time party thereto and MidCap Financial (Ireland) Limited, as agent, arranger and as a lender, and the additional lenders from time to time party thereto, dated May 24, 2019. | Form 6-K | 99.1 | May 28, 2019 | 001-38722 |
| 10.13*# | Forms of award agreements under the 2018 Share Option and Incentive Plan. | | | | |
| 10.14*# | Employment Agreement between the registrant, Orchard Therapeutics North America, and Mark Rothera, effective May 30, 2019. | | | | |

| | | | | | |
|----------|---|-----------|------|---------------|-----------|
| 10.15*# | Employment Agreement between the registrant, Orchard Therapeutics North America, and Frank Thomas, effective September 1, 2019. | | | | |
| 10.16*# | Contract of Employment between Orchard Therapeutics (Europe) Limited and Hubert Gaspar, dated January 8, 2018, as amended effective May 24, 2019. | | | | |
| 16.1 | Letter of Blick Rothenberg Audit LLP, dated March 19, 2019 regarding changes in Registrant's certifying accountants. | Form 20-F | 4.13 | Mar. 22, 2019 | 001-38722 |
| 16.2 | Letter of PricewaterhouseCoopers LLP (UK), dated November 13, 2019 regarding changes in Registrant's certifying accountants. | Form 6-K | 16.1 | Nov. 13, 2019 | 001-38722 |
| 21.1* | List of Subsidiaries. | | | | |
| 23.1* | Consent of PricewaterhouseCoopers LLP, a Delaware limited liability partnership | | | | |
| 23.2* | Consent of PricewaterhouseCoopers LLP, a United Kingdom entity | | | | |
| 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* | XBRL Instance Document | | | | |
| 101.SCH* | XBRL Taxonomy Extension Schema Document | | | | |
| 101.CAL* | XBRL Taxonomy Extension Calculation Linkbase Document | | | | |
| 101.DEF* | XBRL Taxonomy Extension Definition Linkbase Document | | | | |
| 101.LAB* | XBRL Taxonomy Extension Label Linkbase Document | | | | |
| 101.PRE* | XBRL Taxonomy Extension Presentation Linkbase Document | | | | |

* Filed herewith.

† Confidential treatment has been requested 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 have been omitted because they are both (i) not material and (ii) would likely cause competitive harm to the registrant if publicly disclosed.

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

Item 16. Form 10-K Summary

None.

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: February 27, 2020

By: /s/ Mark Rothera
Mark Rothera
President and Chief Executive Officer

POWER OF ATTORNEY

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

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

| <u>Signature</u> | <u>Title</u> | <u>Date</u> |
|---|---|-------------------|
| <u>/s/ Mark Rothera</u> Mark Rothera | President, Chief Executive Officer and Director (Principal Executive Officer) | February 27, 2020 |
| <u>/s/ Frank E. Thomas</u> Frank E. Thomas | Chief Financial Officer and Chief Operating Officer (Principal Financial Officer and Principal Accounting Officer) | February 27, 2020 |
| <u>/s/ James A. Geraghty</u> James A. Geraghty | Chairman of the Board of Directors | February 27, 2020 |
| <u>/s/ Steven M. Altschuler</u> Steven M. Altschuler, M.D. | Director | February 27, 2020 |
| <u>/s/ Joanne T. Beck</u> Joanne T. Beck, Ph.D. | Director | February 27, 2020 |
| <u>/s/ John Curnutte</u> John Curnutte, M.D., Ph.D. | Director | February 27, 2020 |
| <u>/s/ Marc Dunoyer</u> Marc Dunoyer | Director | February 27, 2020 |
| <u>/s/ Jon Ellis</u> Jon Ellis, Ph.D. | Director | February 27, 2020 |

| | | |
|---|----------|-------------------|
| <u>/s/ Bobby Gaspar</u> Bobby Gaspar, M.D., Ph.D. | Director | February 27, 2020 |
| <u>/s/ Charles A. Rowland, Jr.</u> Charles A. Rowland, Jr. | Director | February 27, 2020 |
| <u>/s/ Alicia Secor</u> Alicia Secor | Director | February 27, 2020 |

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

| | December 31, | |
|--|-------------------|-------------------|
| | 2019 | 2018 |
| Assets | | |
| Current assets: | | |
| Cash and cash equivalents | \$ 19,053 | \$ 335,844 |
| Marketable securities | 305,937 | — |
| Trade receivables | 1,442 | 2,103 |
| Prepaid expenses and other current assets | 8,530 | 6,985 |
| Research and development tax credit receivable | 14,934 | 10,585 |
| Total current assets | <u>349,896</u> | <u>355,517</u> |
| Non-current assets: | | |
| Operating lease right-of-use-assets | 19,415 | — |
| Property and equipment, net | 7,596 | 5,476 |
| Research and development tax credit receivable, net of current portion | 13,710 | — |
| Restricted cash | 4,264 | 3,837 |
| Other long-term assets | 4,400 | 1,212 |
| Total non-current assets | <u>49,385</u> | <u>10,525</u> |
| Total assets | <u>\$ 399,281</u> | <u>\$ 366,042</u> |
| Liabilities and shareholders' equity | | |
| Current liabilities: | | |
| Accounts payable | \$ 11,984 | \$ 18,125 |
| Accrued expenses and other current liabilities | 37,980 | 29,780 |
| Operating lease liabilities | 5,892 | — |
| Total current liabilities | <u>55,856</u> | <u>47,905</u> |
| Long-term debt, net | 24,699 | — |
| Operating lease liabilities, net of current portion | 15,320 | — |
| Other long-term liabilities | 4,213 | 6,799 |
| Total liabilities | <u>100,088</u> | <u>54,704</u> |
| Commitments and contingencies (Note 14) | | |
| 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, 2019 and 2018, respectively; 96,923,729 and 85,865,557 shares issued and outstanding at December 31, 2019 and 2018, respectively. | 12,331 | 10,924 |
| Additional paid-in capital | 738,481 | 587,490 |
| Accumulated other comprehensive income | 2,042 | 3,163 |
| Accumulated deficit | (453,661) | (290,239) |
| Total shareholders' equity | <u>299,193</u> | <u>311,338</u> |
| Total liabilities and shareholders' equity | <u>\$ 399,281</u> | <u>\$ 366,042</u> |

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

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

| | Year Ended December 31, | | |
|---|-------------------------|--------------|-------------|
| | 2019 | 2018 | 2017 |
| Product sales, net | \$ 2,513 | \$ 2,076 | \$ — |
| Costs and operating expenses | | | |
| Cost of product sales | 805 | 422 | — |
| Research and development | 117,363 | 205,319 | 32,527 |
| Selling, general and administrative | 57,218 | 31,366 | 5,985 |
| Total costs and operating expenses | 175,386 | 237,107 | 38,512 |
| Loss from operations | (172,873) | (235,031) | (38,512) |
| Other income (expense): | | | |
| Interest income | 7,362 | 1,116 | — |
| Interest expense | (1,538) | — | — |
| Other income (expense), net | 1,387 | 4,390 | (1,179) |
| Total other income (expense), net | 7,211 | 5,506 | (1,179) |
| Net loss before income tax | (165,662) | (229,525) | (39,691) |
| Income tax benefit (expense) | 2,240 | (970) | (53) |
| Net loss attributable to ordinary shareholders | \$ (163,422) | \$ (230,495) | \$ (39,744) |
| Net loss per share attributable to ordinary shareholders, basic and diluted | \$ (1.75) | \$ (10.22) | \$ (4.48) |
| Weighted average number of ordinary shares outstanding, basic and diluted | 93,240,355 | 22,559,389 | 8,872,768 |
| Other comprehensive (loss) income | | | |
| Foreign currency translation adjustment | (1,387) | (964) | 4,398 |
| Unrealized gain (loss) on marketable debt securities | 266 | — | — |
| Total other comprehensive (loss) income | (1,121) | (964) | 4,398 |
| Total comprehensive loss | \$ (164,543) | \$ (231,459) | \$ (35,346) |

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

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

| | Convertible preferred shares | | Convertible preferred shares | | Ordinary shares | | Additional paid-in capital | Accumulated other comprehensive income (loss) | Accumulated deficit | Total |
|---|------------------------------|------------------|------------------------------|-------------------|-------------------|------------------|----------------------------|---|---------------------|-------------------|
| | Shares | Amount | Shares | Amount | Shares | Amount | | | | |
| Balance at December 31, 2016 | 11,204,199 | \$ 16,970 | — | \$ — | 957 | \$ 957 | \$ 2,790 | \$ (271) | \$ (20,000) | \$ (16,524) |
| Issuance of convertible preferred shares, net of issuance costs | 14,693,207 | 66,981 | — | — | — | — | — | — | — | — |
| Reclassification of convertible preferred shares from temporary equity to permanent equity | (25,897,406) | (83,951) | 25,897,406 | 83,951 | — | — | — | — | — | 83,951 |
| Issuance of convertible preferred shares, net of issuance costs | — | — | 7,380,272 | 50,118 | — | — | 1,019 | — | — | 50,118 |
| Share-based compensation expense | — | — | — | — | — | — | — | — | — | 1,019 |
| Ordinary shares committed to be issued as part of license agreements | — | — | — | — | — | — | 1,534 | — | — | 1,534 |
| Ordinary shares issued as part of license agreements | — | — | — | — | 188 | 1,465 | — | — | — | 1,653 |
| Foreign currency translation adjustment | — | — | — | — | — | — | — | 4,398 | — | 4,398 |
| Net loss | — | — | — | — | — | — | — | — | (39,744) | (39,744) |
| Balance at December 31, 2017 | — | \$ — | 33,277,678 | \$ 134,069 | 8,927,121 | \$ 1,145 | \$ 6,808 | \$ 4,127 | \$ (59,744) | \$ 86,405 |
| Issuance of convertible preferred shares, net of issuance costs | — | — | 26,891,222 | 242,744 | — | — | — | — | — | 242,744 |
| Share-based compensation expense | — | — | — | — | — | — | 6,766 | — | — | 6,766 |
| Exercise of share options | — | — | — | — | 2 | 2 | — | — | — | 28 |
| Ordinary shares issued as part of license agreements | — | — | — | — | 83 | 1,302 | — | — | — | 1,385 |
| Effect of corporate reorganization, including conversion of preferred shares to ordinary shares | — | — | (60,168,900) | (376,813) | 7,647 | 7,647 | 369,166 | — | — | — |
| Issuance of ADSs in initial public offering, net of issuance costs of \$4,200 | — | — | — | — | 16,103,572 | 2,047 | 203,422 | — | — | 205,469 |
| Foreign currency translation adjustment | — | — | — | — | — | — | — | (964) | — | (964) |
| Net loss | — | — | — | — | — | — | — | — | (230,495) | (230,495) |
| Balance at December 31, 2018 | — | \$ — | — | \$ — | 10,924 | \$ 10,924 | \$ 587,490 | \$ 3,163 | \$ (290,239) | \$ 311,338 |
| Share-based compensation expense | — | — | — | — | — | — | 19,424 | — | — | 19,424 |
| Exercise of share options | — | — | — | — | 158 | 1,845 | — | — | — | 2,003 |
| Issuance of ESPP shares | — | — | — | — | 16 | 1,290 | — | — | — | 1,306 |
| Issuance of ADSs in follow-on offering, net of issuance costs of \$605 | — | — | — | — | 9,725,268 | 1,233 | 128,432 | — | — | 129,665 |
| Foreign currency translation adjustment | — | — | — | — | — | — | — | (1,387) | — | (1,387) |
| Unrealized gain on marketable debt securities | — | — | — | — | — | — | — | 266 | — | 266 |
| Net loss | — | — | — | — | — | — | — | — | (163,422) | (163,422) |
| Balance at December 31, 2019 | — | \$ — | — | \$ — | 96,923,729 | \$ 12,331 | \$ 738,481 | \$ 2,042 | \$ (453,661) | \$ 299,193 |

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

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

| | Year Ended December 31, | | |
|--|-------------------------|--------------|-------------|
| | 2019 | 2018 | 2017 |
| Cash flows from operating activities | | | |
| Net loss attributable to ordinary shareholders | \$ (163,422) | \$ (230,495) | \$ (39,744) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | |
| Depreciation expense | 1,675 | 1,199 | 302 |
| Share-based compensation | 19,424 | 6,766 | 1,019 |
| Non-cash interest expense | 311 | — | — |
| Amortization of provision on loss contract | (3,855) | (6,300) | — |
| Non-cash consideration for licenses and milestones | — | 94,776 | 3,126 |
| Amortization of (discount) premium on marketable securities | (676) | — | — |
| Unrealized foreign currency gains | (1,859) | — | — |
| Changes in operating assets and liabilities: | | | |
| Trade receivables | 715 | (927) | — |
| Research and development tax credit receivable | (17,564) | (10,079) | (152) |
| Prepays and other assets | (5,151) | (5,867) | (3,753) |
| Operating leases, right-of-use-assets | 3,064 | — | — |
| Accounts payable | (6,413) | 14,848 | 1,930 |
| Accrued expenses and other current liabilities | 11,434 | 31,663 | 4,672 |
| Other long-term liabilities | (1,424) | 6,880 | 113 |
| Operating lease liabilities | (2,390) | — | — |
| Net cash used in operating activities | \$ (166,131) | \$ (97,536) | \$ (32,487) |
| Cash flows from investing activities | | | |
| Proceeds from sales and maturities of marketable securities | 109,019 | — | — |
| Purchases of marketable securities | (414,010) | — | — |
| Purchases of property and equipment | (4,367) | (4,032) | (1,559) |
| Net cash used in investing activities | \$ (309,358) | \$ (4,032) | \$ (1,559) |
| Cash flows from financing activities | | | |
| Issuance of debt from credit facility, net of issuance costs | 24,466 | — | — |
| Issuance of convertible preferred shares, net of issuance costs | — | 149,367 | 115,696 |
| Issuance of ADRs in public offerings | 130,270 | 209,669 | — |
| Payment of offering costs | (605) | (4,200) | — |
| Proceeds from employee equity plans | 3,322 | 28 | — |
| Net cash provided by financing activities | \$ 157,453 | \$ 354,864 | \$ 115,696 |
| Effect of exchange rate changes on cash | 1,672 | (3,471) | 4,709 |
| Net increase (decrease) in cash and restricted cash | \$ (316,364) | \$ 249,825 | \$ 86,359 |
| Cash and restricted cash—beginning of year | 339,681 | 89,856 | 3,497 |
| Cash, cash equivalents, and restricted cash—end of year | \$ 23,317 | \$ 339,681 | \$ 89,856 |
| Supplemental disclosure of non-cash investing and financing activities | | | |
| Settlement of tranche obligations | — | — | 1,402 |
| Property and equipment included in accrued expenses and accounts payable at period end | 647 | — | 1,247 |
| Convertible preferred shares issued for licenses | — | 93,391 | — |
| Supplemental disclosure of cash flow information | | | |
| Cash paid for interest | 1,227 | — | — |
| Cash paid for taxes | 1,474 | — | — |

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

Orchard Therapeutics plc
Notes to Consolidated Financial Statements

1. Nature of Business and Basis of Presentation

Orchard Therapeutics plc and its subsidiaries (the “Company”) is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. The Company’s *ex vivo* autologous gene therapy approach utilizes genetically-modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Company is advancing seven clinical-stage programs across multiple therapeutic areas, including inherited neurometabolic disorders, primary immune deficiencies and blood disorders, where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

The Company is a public limited company incorporated pursuant to the laws of England and Wales. Orchard Therapeutics plc (formerly Orchard Rx Limited) was originally incorporated under the laws of England and Wales in August 2018 to become a holding company for Orchard Therapeutics Limited. Orchard Therapeutics 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.

Pursuant to a corporate reorganization, all the interests in Orchard Therapeutics Limited were exchanged for the same number and class of newly issued shares of Orchard Rx Limited and, as a result, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited. On October 29, 2018, Orchard Rx Limited re-registered as a public limited company and changed its name to Orchard Therapeutics plc and Orchard Therapeutics Limited changed its name to Orchard Therapeutics (Europe) Limited.

On November 1, 2018, the Company’s different classes of preferred shares and our ordinary shares were consolidated on a one-for-0.8003 basis. Following the share consolidation, each share was re-designated as an ordinary share on a one-for-one basis. Accordingly, all share and per share amounts for all periods presented in the consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the reverse stock split.

As part of the corporate reorganization as described above, each ordinary share with a nominal value of £0.00001 was redenominated as an ordinary share with a nominal value of £0.10. Accordingly, equity accounts for all periods presented in the consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the effects of the redenomination of the Company’s ordinary shares.

On November 2, 2018, the Company closed its initial public offering (IPO) of American Depositary Shares (“ADS”) in which the Company sold an aggregate of 16,103,572 ADSs representing the same number of ordinary shares at a public offering price of \$14.00 per ADS. Net proceeds were \$205.5 million, after deducting underwriting discounts and commissions of \$15.8 million and offering expenses of \$4.2 million paid by the Company.

In June 2019, the Company completed a follow-on public offering of ADSs in which the Company sold an aggregate of 9,725,268 ADSs representing the same number of ordinary shares at a public offering price of \$14.25 per ADS. Net proceeds were \$129.7 million, after deducting underwriting discounts and commissions of \$8.3 million and offering expenses of \$0.6 million paid by the Company.

Orchard Therapeutics plc is a continuation of Orchard Therapeutics Limited and its subsidiaries, and the corporate reorganization has been accounted for as a combination of entities under common control. The corporate reorganization has been given retrospective effect in these financial statements and such financial statements represent the financial statements of Orchard Therapeutics Limited for all periods prior to the corporate reorganization. In connection with the corporate reorganization, outstanding share option awards of Orchard Therapeutics Limited were exchanged for share awards and option grants of Orchard Therapeutics plc with identical terms and restrictions.

The Company is subject to risks and uncertainties common to development-stage companies in the biotechnology industry. There can be no assurance that the Company’s research and development will be successfully completed, that adequate protection for the Company’s technology will be obtained, that any products developed will obtain necessary government regulatory approval or that any products, if approved, will be commercially viable. The Company operates in an environment of rapid technological innovation and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and service providers. Even if the

Company's product development efforts are successful in gaining regulatory approval, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Through December 31, 2019, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares and ADSs in the IPO and follow-on offering. The Company has incurred recurring losses since its inception, including net losses of \$163.4 million, \$230.5 million and \$39.7 million, for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, the Company had an accumulated deficit of \$453.7 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expects that its cash, cash equivalents, and marketable securities on hand as of December 31, 2019 of \$325.0 million, will be sufficient to fund its operations and capital expenditure requirements through at least the next twelve months. The Company will seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into collaborations or other arrangements. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Basis of presentation

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

2. Summary of Significant Accounting Policies

Use of estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the research and development tax credit receivable, the Strimvelis loss provision, the fair values of ordinary and convertible preferred shares, share-based compensation, operating lease assets and liabilities, and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Concentration of credit risk

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

Foreign currency translation

The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises capital and expends cash in U.S. dollars. The functional currency of our subsidiary operations is the applicable local currency. Transactions in foreign currencies are translated into the functional currency of the subsidiary in which they occur at the foreign exchange rate in effect on at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are translated into the functional currency of the relevant subsidiary at the foreign exchange rate in effect on the balance sheet date. Non-monetary assets and liabilities denominated in foreign currencies that differ from the functional currency are translated into the functional currency at the exchange rates prevailing at the date of the transaction. The Company recorded a foreign currency transaction gain of \$1.5 million, and \$4.4 million for the years ended December 31, 2019 and 2018,

respectively, and a foreign currency transaction loss of \$1.2 million for the year ended December 31, 2017, respectively, which is included in other income (expense) in the statements of operations and comprehensive loss.

The results of operations for subsidiaries, whose functional currency is not the U.S. dollar, are translated at an average rate for the period where this rate approximates the prevailing foreign exchange rates at the dates of the transactions and the balance sheet of these subsidiaries are translated at prevailing foreign exchange rates at the balance sheet date. Exchange differences arising from this translation of foreign operations are reported as a component of other comprehensive income (loss).

Cash and cash equivalents

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

Marketable securities

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

The Company evaluates its investments with unrealized losses for other-than-temporary impairment. When assessing investments for other-than-temporary declines in value, the Company considers such factors as, among other things, how significant the decline in value is as a percentage of the original cost, how long the market value of the investment has been less than its original cost, the Company's ability and intent to retain the investment for a period of time sufficient to allow for any anticipated recovery in fair value and market conditions in general. If any adjustment to fair value reflects a decline in the value of the investment that the Company considers to be "other than temporary," the Company reduces the investment to fair value through a charge to the statement of operations and comprehensive loss. No such adjustments were necessary during the periods presented.

Restricted Cash

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on our consolidated balance sheet. The Company's lease for the Fremont manufacturing facility requires a letter of credit of \$3.0 million at December 31, 2019. The Company is also contractually required to maintain a cash collateral account associated with corporate credit cards and other leases in the amount of \$1.3 million at December 31, 2019. The Company includes the restricted cash balance in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the consolidated statements of cash flows. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported in the consolidated balance sheet that sum to the total of the amounts reported in the consolidated statement of cash flows (in thousands):

| | December 31, | |
|---|---------------------|-------------------|
| | 2019 | 2018 |
| Cash and cash equivalents | \$ 19,053 | \$ 335,844 |
| Restricted cash | 4,264 | 3,837 |
| Total cash, cash equivalents and restricted cash shown in the statement of cash flows | <u>\$ 23,317</u> | <u>\$ 339,681</u> |

Property and equipment

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

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

As of December 31, 2019, and 2018, the Company's property and equipment consisted of furniture and fixtures, office and computer equipment, lab equipment and leasehold improvements. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts, and any resulting gain or loss is included in the statement of operations and other comprehensive loss. Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property and equipment, are expensed as incurred.

Impairment of long-lived assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, as determined in accordance with the related accounting literature. To date, the Company has not recorded any impairment losses on long-lived assets.

Fair value measurements

Certain assets and liabilities of the Company are carried at fair value under U.S. GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. 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—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in 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 carrying values of the Company's trade receivables, other receivables, accounts payable, accrued expenses and other current liabilities approximate their fair values due to the short-term nature of these assets and liabilities.

Segment information

Operating segments are defined as components of an enterprise for which separate discrete information is available for evaluation by the chief operating decision maker in deciding how to allocate resources and assess performance. The Company and the Company's chief operating decision maker, the Company's Chief Executive Officer, views the Company's operations and manages its business as a single operating segment, which is focused on discovering, acquiring, developing and commercializing gene therapies for patients with rare disorders. The Company operates in three geographic regions: the United Kingdom, European Union, and United States. The Company had property and equipment of \$2.6 million and \$5.0 million located in the United Kingdom and United States, respectively, as of December 31, 2019. The Company had property and equipment of \$1.7 million and \$3.8 million located in the United Kingdom and United States, respectively, as of December 31, 2018. The Company had right-of-use assets of \$3.7 million in the United Kingdom and European Union and \$15.7 million in the United States as of December 31, 2019. The Company had product sales of \$2.5 million and \$2.1 million in 2019 and 2018, respectively, all of which originated in the European Union.

Research and development costs

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

Research contract costs and accruals

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

Share-based compensation

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

Prior to the adoption of Accounting Standards Update ("ASU") No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"), which is discussed below under "Recently adopted accounting pronouncements," the measurement date for non-employee awards was generally the date the services were completed, resulting in financial reporting period adjustments to share-based compensation during the vesting terms for changes in the fair value of the awards. At the end of each financial reporting period prior to completion of the service period, the fair value of the unvested awards was remeasured using the then-current fair value of the Company's ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model.

After adoption of ASU 2018-07, the measurement date for non-employee awards is the date of the grant. The compensation expense for non-employees is recognized, without changes in the fair value of the award, over the requisite service period, which is the vesting period of the respective award.

The Company classifies share-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Valuation of Stock Options

The fair value of each option is estimated on the date of grant using the Black-Scholes option pricing model. Assumptions used in the option pricing model include the following:

Expected volatility. The Company estimates its expected share price volatility based on the historical volatility of publicly traded peer companies and expects to continue to do so until it has adequate historical data regarding the volatility of its own traded share price.

Expected term. The expected term of the Company's share options has been determined utilizing the "simplified method" for awards that qualify as "plain-vanilla" options.

Risk-free interest rate. The risk-free interest rate is determined by reference to the United States 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. Expected dividend yield is based on the Company's history of not paying cash dividends on ordinary shares. The Company does not expect to pay any cash dividends in the foreseeable future.

Fair value of ordinary shares. Options granted subsequent to the Company's IPO are issued with an exercise price equal to the fair market value of the Company's ADS at the date of grant.

Valuation of RSUs

We estimate the fair value of our performance-based restricted stock unit ("RSUs") awards or components of RSU awards whose vesting is contingent upon market conditions, such as volume weighted-average price ("VWAP"), using the Monte-Carlo simulation model. The fair value of RSUs or components of RSU awards where vesting is contingent upon market conditions is amortized based upon the estimated derived service period. The fair value of RSUs or components of RSUs granted to our employees and directors is determined, where vesting is dependent on future services or regulatory or research and development milestones, based upon the quoted closing market price per share on the date of grant.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in shareholders' equity (deficit) that result from transactions and economic events other than those with shareholders. For the years ended December 31, 2019, 2018 and 2017, the components of accumulated other comprehensive loss are detailed as follows (in thousands):

| | Currency Translation Adjustment | Unrealized Gain (Loss) on Marketable Securities | Accumulated Other Comprehensive Income (Loss) |
|---|---------------------------------------|---|--|
| Balance at December 31, 2016 | \$ (271) | \$ — | \$ (271) |
| Other comprehensive (loss) income, net of tax | 4,398 | — | 4,398 |
| Balance at December 31, 2017 | \$ 4,127 | \$ — | \$ 4,127 |
| Other comprehensive (loss) income, net of tax | (964) | — | (964) |
| Balance at December 31, 2018 | \$ 3,163 | \$ — | \$ 3,163 |
| Other comprehensive (loss) income, net of tax | (1,387) | 266 | (1,121) |
| Balance at December 31, 2019 | <u>\$ 1,776</u> | <u>\$ 266</u> | <u>\$ 2,042</u> |

Leases

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

As the Company's leases do not provide an implicit rate, the Company utilized the appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment. The Company estimated the incremental borrowing rate based on the Company's currently outstanding credit facility as inputs to the analysis to calculate a spread, adjusted for factors that reflect the profile of secured borrowing over the expected term of the lease.

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

Strimvelis loss provision

As part of the GSK transaction, the Company is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available (Note 11). 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 Strimvelis and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a credit to research and development expense. We have made an estimate of the expected future losses associated with Strimvelis and adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of the future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for the updated future losses. The following table below outlines the changes to the Strimvelis loss provision for the periods ended December 31, 2019 and 2018 (in thousands):

| | Twelve Months Ended | |
|--------------------------------|---------------------|-----------|
| | December 31, | |
| | 2019 | 2018 |
| Balance at beginning of period | \$ 10,339 | \$ - |
| Provisions | — | 18,351 |
| Amortization of loss provision | (3,855) | (6,366) |
| Foreign currency translation | 306 | (1,646) |
| Balance at end of period | \$ 6,790 | \$ 10,339 |

As of December 31, 2019, \$3.0 million of the Strimvelis loss provision was classified as current, and \$3.8 million was classified as non-current. As of December 31, 2018, \$4.2 million of the Strimvelis loss provision was classified as current, and \$6.1 million was classified as non-current.

United Kingdom Research and development income tax credits

As a company that carries out research and development activities, the Company is able to submit tax credit claims from two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit (“SME”) program and the Research and Development Expenditure Credit (“RDEC”) program depending on eligibility. Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income.

Each reporting period, management evaluates which tax relief programs the Company is expected to be eligible for and records a reduction to research and development expense for the portion of the expense that it expects to qualify under the programs, that it plans to submit a claim for, and it has reasonable assurance that the amount will ultimately be realized. Based on criteria established by HM Revenue and Customs (“HMRC”), management of the Company expects a proportion of expenditures being carried in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for the research and development tax relief programs for the years ended December 31, 2019, 2018 and 2017.

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

The Company recognizes credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expense.

The Company has recorded a U.K. research and development tax credit as an offset to research and development expense in the consolidated statements of operations and comprehensive loss of \$17.6 million, \$10.2 million and \$0.7 million, for the years ended December 31, 2019, 2018 and 2017, respectively. During 2019, the Company recorded \$4.1 million related to a change in estimate associated with our U.K. research and development tax credit from prior years. The change in estimate was based on the results of a tax credit analysis associated with our qualified projects and research and development expenditures. This amount was recorded as an offset to research and development expense in 2019.

As of December 31, 2019, the Company’s tax incentive receivable from the U.K. was \$28.6 million, of which \$14.9 million was classified as current and \$13.7 million was classified as non-current. As of December 31, 2018, the Company’s tax incentive receivable from the U.K. was \$10.6 million, all of which was classified as current. The effects of foreign currency translation increased the receivable by \$0.7 million in 2019 and decreased the receivable by \$0.5 million in 2018. As of December 31, 2019, the Company has received amounts totaling \$0.2 million associated with our 2016 tax incentive claim with HMRC.

Income taxes

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

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

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

for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate, as well as the related net interest and penalties.

Product sales

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

Net income (loss) per share

The Company follows the two-class method when computing net income (loss) per share as the Company has issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of ordinary and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to ordinary shareholders for the period to be allocated between ordinary and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net income (loss) per share attributable to ordinary shareholders is computed by dividing the net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period. Diluted net income (loss) attributable to ordinary shareholders is computed by adjusting net income (loss) attributable to ordinary shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to ordinary shareholders is computed by dividing the diluted net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period, including potential dilutive ordinary shares. For purpose of this calculation, outstanding options and convertible preferred shares are considered potential dilutive ordinary shares.

The Company's convertible preferred shares contractually entitle the holders of such shares to participate in dividends but do not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss attributable to ordinary shareholders, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to ordinary shareholders, diluted net loss per share attributable to ordinary shareholders is the same as basic net loss per share attributable to ordinary shareholders, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive.

The Company reported a net loss attributable to ordinary shareholders for the years ended December 31, 2019, 2018, and 2017.

Recently adopted accounting pronouncements

In June 2018, the Financial Accounting Standards Board ("FASB") issued ASU No. 2018-07 ("ASU 2018-07"). ASU 2018-07 expands the scope of Topic 718, Compensation—Stock Compensation, to include share-based payments issued to nonemployees for goods or services. Consequently, the accounting for share-based payments to nonemployees and employees will be substantially aligned. ASU 2018-07 supersedes Subtopic 505-50, Equity—Equity-Based Payments to Non-Employees. The amendments are effective for public companies for fiscal years beginning after December 15, 2018, including interim periods within that fiscal year. For all other companies, the amendments are effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted, but no earlier than a company's adoption date of Topic 606. ASU 2018-07 was adopted as of January 1, 2017 and did not have a material impact on the Company's financial position, results of operations or cash flows.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). ASU 2016-02 supersedes the lease guidance under FASB ASC Topic 840, *Leases*, resulting in the creation of FASB ASC

Topic 842, *Leases* (“ASC 842”). The new standard requires that all lessees (i) recognize, on the balance sheet, liabilities to remit lease payments and right-of-use assets, representing the right to use the underlying asset for the lease term for both finance and operating leases, and (ii) disclose qualitative and quantitative information about its leasing arrangements.

In July 2018, the FASB issued ASU 2018-10, *Codification Improvements to Topic 842, Leases* (“ASU 2018-10”) and ASU 2018-11, *Leases (Topic 842) Targeted Improvements* (“ASU 2018-11”), which added an optional transition method under which financial statements may be prepared under the revised guidance for the year of adoption, but not for prior years. Under the latter method, entities will recognize a cumulative catch-up adjustment to the opening balance of retained earnings in the period of adoption.

As we are no longer an emerging growth company, ASC 842 became effective for us in 2019. The Company adopted ASC 842 using the modified retrospective approach with an effective date of January 1, 2019 for leases that existed on that date. Prior period results continue to be presented under ASC 840 based on the accounting standards originally in effect for such periods. This standard provides a number of optional practical expedients in transition. The Company applied the package of practical expedients to leases that commenced prior to the effective date, whereby it elected not to reassess the following: (i) whether any expired or existing contracts contain leases; (ii) the lease classification for any expired or existing leases; and (iii) initial direct costs for any existing leases. The Company elected the short-term lease recognition exemption for all leases that qualify, where a right-of-use asset or lease liability will not be recognized for short term leases that have terms of one year or less.

The operating lease right-of-use assets and corresponding liabilities relate to existing facility operating leases in London, UK, Boston, Massachusetts, and the San Francisco Bay Area, California, as well as an embedded operating lease for research and development space at a contract manufacturing organization. The most significant effects of adoption were the recognition of material new right-of-use assets and corresponding liabilities on its consolidated balance sheet related to its existing facility operating leases (see Note 7). The adoption of this standard has had a material impact on the Company’s financial position but did not significantly affect the Company’s results of operations or cash flows. The following table summarizes the financial impact on the Company’s consolidated balance sheet upon recording of the adoption entries for ASU 2016-02 on January 1, 2019 (in thousands):

| | January 1, 2019 Prior to ASC 842 Adoption | ASC 842 Adjustment | January 1, 2019 as Adjusted |
|---|--|-----------------------|--------------------------------|
| Consolidated balance sheet data (in thousands): | | | |
| Operating lease right-of-use assets | \$ — | \$ 22,348 | \$ 22,348 |
| Prepaid rent (1) | 373 | (373) | — |
| Deferred rent (2) | 181 | (181) | — |
| Deferred rent, non-current (3) | 357 | (357) | — |
| Operating lease liabilities | — | 3,746 | 3,746 |
| Operating lease liabilities, net of current portion | — | 18,748 | 18,748 |

- (1) Included in Prepaid expenses and other current assets in 2018 consolidated balance sheet
- (2) Included in Accrued expenses and other current liabilities in 2018 consolidated balance sheet
- (3) Included in Other long-term liabilities in 2018 consolidated balance sheet

In May 2017, the FASB issued ASU No. 2017-09, *Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting* (“ASU 2017-09”), which clarifies when to account for a change to the terms or conditions of a share-based payment award as a modification. Under the new guidance, modification accounting is required only if the fair value, the vesting conditions or the classification of the award (as equity or liability) changes as a result of the change in terms or conditions. ASU 2017-09 is effective for all entities for annual periods, and interim periods within those annual periods, beginning after December 15, 2017. Early adoption is permitted, including adoption in any interim period, for 1) public business entities for reporting periods for which financial statements have not yet been issued and 2) all other entities for reporting periods for which financial statements have not yet been made available for issuance. The Company adopted ASU 2017-09 as of January 1, 2018. The adoption of ASU 2017-09 did not have a material impact on the Company’s financial position, results of operations or cash flows.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* (“ASU 2016-18”), which requires companies to include amounts generally described as restricted cash and restricted cash equivalents in

cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The Company adopted ASU 2016-18 for annual period beginning after December 15, 2017. Prior to the adoption of ASU 2016-18, the Company did not have material balances meeting the definition of restricted cash or restricted cash equivalents.

In August 2016, the FASB issued Accounting Standards Update No 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments* (“ASU 2016-15”) to clarify guidance on the classification of certain cash receipts and payments in the statement of cash flows. The Company adopted this guidance as of January 1, 2018. The adoption of ASU 2016-15 did not have a material impact on the Company’s financial statements.

In October 2016, the FASB issued ASU No. 2016-16, *Income Taxes (Topic 740): Intra-Entity Transfer of Assets Other than Inventory* (“ASU 2016-16”), which requires the recognition of the income tax consequences of an intra-entity transfer (sales) of an asset, other than inventory, when the transfer occurs. The standard is effective for the Company beginning January 1, 2018. The Company does not currently engage in sale transactions with its wholly owned subsidiaries. Adoption of this standard did not have a material impact on the Company’s consolidated financial statements.

In January 2016, the FASB issued ASU 2016-01, *Financial Instruments – Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities* (“ASU 2016-01”), which amended the guidance on the recognition and measurement of financial assets and financial liabilities. The new guidance requires that equity investments (except those accounted for under the equity method of accounting, or those that result in consolidation of the investee) are measured at fair value with changes in fair value recognized in net income. The guidance also requires the use of an exit price when measuring the fair value of financial instruments for disclosure purposes, eliminates the requirement to disclose the methods and significant assumptions used to estimate the fair value that is required to be disclosed for financial instruments measured at amortized cost and requires separate presentation of financial assets and financial liabilities by measurement category and form of financial asset. The guidance became effective for the fiscal year beginning January 1, 2018, including interim periods within that fiscal year. Adoption of ASU 2016-01 did not have a material impact on the Company’s consolidated financial statements as the Company does not hold any equity securities.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* (“ASU 2014-09”), which supersedes existing revenue recognition guidance under U.S. GAAP. The standard’s core principle is that a company will recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods or services. The standard defines a five-step process to achieve this principle and will require companies to use more judgment and make more estimates than under the current guidance. The Company expects that these judgments and estimates will include identifying performance obligations in the customer contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts. In August 2015, the FASB issued ASU 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date*, which delays the effective date of ASU 2014-09 such that the standard is effective for public entities for annual period beginning after December 15, 2017, including interim periods within those fiscal years. For all other entities, the guidance is effective beginning after December 15, 2018, and interim periods within annual periods beginning after December 15, 2019. Early adoption of the standard is permitted for annual periods beginning after December 15, 2016, including interim periods within those fiscal years. The Company adopted these revenue standards on January 1, 2017. Prior to 2018, the Company had no sources of revenue. In 2018, the Company had its first sales of Strimvelis and have applied this guidance to our revenue recognition, and as such there was no impact from the adoption of ASC 606 in prior periods.

Recently issued accounting pronouncements not yet adopted

In June 2016, the FASB issued new accounting guidance which requires entities to record expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities in unrealized loss positions, the new standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard became effective for the Company on January 1, 2020. We currently do not expect this guidance to have a significant impact on our consolidated financial statements and related disclosures.

The Company has considered other recent accounting pronouncements and concluded that they are either not applicable to the business, or that the effect is not expected to be material to the financial statements as a result of future adoption.

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, 2019 and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair value determined by Level 2 inputs utilize observable inputs other than Level 1 prices, such as quoted prices

for similar assets or liabilities, quoted market prices in markets that are not active or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities. Fair values determined by Level 3 inputs are unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. During the year ended December 31, 2019, there were no transfers between Level 1 and Level 2 financial assets.

The following table summarizes the Company's cash equivalents and marketable securities as of December 31, 2019 (in thousands)

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

The Company had no cash equivalents and marketable securities at December 31, 2018.

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

Marketable Securities

The following table summarizes the Company's level 2 cash equivalents and marketable securities as of December 31, 2019, in thousands:

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

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

| | |
|--|-------------------|
| Maturities in one year or less | \$ 250,490 |
| Maturities between one and three years | 68,398 |
| Balance at December 31, 2019 | <u>\$ 318,888</u> |

4. Revenue Recognition

The Company currently has one commercial-stage therapy, Strimvelis, for the treatment of ADA-SCID. Strimvelis is currently administered exclusively at the San Raffaele Hospital in Milan, Italy. San Raffaele Hospital will purchase and pay for Strimvelis and submit a claim to the payer. The Company's contracted sales with San Raffaele Hospital contain a single performance obligation and the Company recognizes revenue from product sales when the Company has satisfied its performance obligation by transferring control of Strimvelis to San Raffaele Hospital. Control of the product generally transfers upon the completion of the scheduled Strimvelis treatment. The Company's product sales represent total gross

product sales of Strimvelis. The Company evaluated the variable consideration under Accounting Standards Codification (ASC) 606, *Revenue from Contracts with Customers*, and there is currently no variable consideration included in the transaction price for Strimvelis. The Company excludes from measurement of the transaction price all taxes assessed by a governmental authority that are both imposed concurrent with the specific revenue-producing transaction and collected by the Company from a customer. The Company does include such taxes in trade receivables on the consolidated balance sheet.

Costs to manufacture the product and those associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates that there is minimal risk of product return, including the risk of product expiration.

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

5. Property and Equipment

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

| | December 31, | |
|--------------------------------|--------------|----------|
| | 2019 | 2018 |
| Property and equipment: | | |
| Lab equipment | \$ 6,377 | \$ 4,689 |
| Leasehold improvements | 1,839 | 1,487 |
| Furniture and fixtures | 508 | 403 |
| Office and IT equipment | 184 | 152 |
| Construction-in-progress | 1,848 | 241 |
| Property and equipment | \$ 10,756 | \$ 6,972 |
| Less: accumulated depreciation | (3,160) | (1,496) |
| Property and equipment, net | \$ 7,596 | \$ 5,476 |

Depreciation expense for the years ended December 31, 2019, 2018 and 2017 was \$1.7 million, \$1.2 million and \$0.3 million, respectively.

6. Accrued Expenses and Other Liabilities

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

| | December 31, | |
|--|--------------|-----------|
| | 2019 | 2018 |
| Accrued external research and development expenses | \$ 16,215 | \$ 12,738 |
| Accrued payroll and related expenses | 12,381 | 7,372 |
| Accrued professional fees | 1,321 | 1,186 |
| Accrued other | 5,069 | 2,762 |
| Strimvelis liability - current portion | 2,994 | 4,170 |
| Due to UCLA | — | 1,552 |
| Total accrued expenses and other current liabilities | \$ 37,980 | \$ 29,780 |

7. Leases

Operating leases

In October 2016, the Company entered into a lease agreement for laboratory space in Foster City, California, United States. The lease had a term of 5 years and originally terminated in October 2021. In June 2019, the Company assigned the lease to a third-party and were relieved of future payment obligations under the lease. Costs associated with the termination of the lease were not material.

In November 2017 and January 2019, the Company entered into lease agreements for office and laboratory space in Menlo Park, California, United States. The leases terminate in December 2020. The combined annual rental payments under both

leases with the same landlord approximate \$1.3 million. The Company was provided with one month of free rent in connection with the first lease. The lease agreement includes annual rent escalation provisions.

In January 2018 and December 2018, the Company entered into lease agreements for office space in London, United Kingdom, both of which terminate in January 2023. The combined annual rental payments under the lease agreements approximate \$0.9 million.

In March 2018, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental payments approximate \$0.3 million. The lease agreement includes annual rent escalation provisions.

In July 2019, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which commences for accounting purposes in January 2020. The lease terminates in September 2026. The annual rental payments approximate \$0.8 million. The lease agreement includes annual rent escalation provisions.

Fremont operating lease agreement

In December 2018, the Company leased manufacturing, laboratory, and office space in Fremont, California (the “Fremont facility”) which terminates in May 2030. The annual rental payments approximate \$2.6 million. The lease includes annual rent escalation provisions. The Company was provided with 8 months of free rent. Subject to the terms of the lease agreement, the Company executed a \$3.0 million letter of credit upon signing the lease, which may be reduced by 25% subject to reduction requirements specified therein. This amount is classified as restricted cash on the consolidated balance sheet.

Upon the adoption of ASU 2016-02, we recorded an operating lease right-of-use asset of \$14.7 million and a corresponding lease liability of \$14.6 million related to the Fremont facility. The lease provides for approximately \$5.0 million in tenant improvement allowances to be reimbursed to the Company by the landlord. These tenant improvement allowances have been included in the calculation of the operating lease liability and is currently expected to be received in 2021. The Company will continue to assess the expected receipt of the tenant improvement allowances.

The Company intends to perform non-normal tenant improvements to the property to customize the facility to suit the Company’s unique manufacturing needs. The Company is responsible for paying directly the costs associated with the construction project. As of December 31, 2019, the Company has not broken ground or incurred significant costs associated with the construction.

Upon the start of construction, the Company is required to deposit \$10.0 million in an escrow account. Subject to the terms of the lease and reduction provisions, this amount may be decreased to nil over time. As of December 31, 2019, the Company has no funds deposited in the escrow account.

Embedded operating lease arrangement

The Company is party to a manufacturing agreement for research and development and future commercial production with a contract manufacturing organization. The agreement with the contract manufacturing organization was novated to the Company as part of the GSK Agreement (see Note 11). The agreement contains an operating lease for the use of dedicated manufacturing suites. Prior to the novation of the contract, GSK paid the contract manufacturing organization upfront fees of €6.8 million for license costs and manufacturing suite GMP readiness upon the achievement of certain contractual milestones. After novation of the contract to the Company as part of the GSK Agreement, the Company gained the ability to control the underlying manufacturing suites.

The Company makes bi-annual pre-payments to the contract manufacturing organization for manufacturing costs. The fair value of the lease component of the agreement was determined utilizing information from the agreement about the value of the suites, and a portion of the pre-payment amount is allocated to the lease component. With the adoption of ASU 2016-02, the Company recorded a right-of-use asset and corresponding lease liability for the operating lease in the amounts of \$2.0 million and \$2.0 million, respectively. As of December 31, 2019, the agreement with the contract manufacturing organization extends until July 1, 2022.

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 costs recognized under ASC 842 and other information pertaining to the Company's operating leases as of December 31, 2019 (in thousands):

| | | |
|--|----|--------------|
| Fixed lease cost | \$ | 5,589 |
| Variable lease cost | | 1,436 |
| Total lease cost | \$ | <u>7,025</u> |
| Other information | | |
| Operating cash flows used for operating leases | | 5,738 |
| Weighted-average remaining lease term (years) | | 8.2 |
| Weighted-average discount rate | | 9.3% |

During the year ended December 31, 2019 there were no material right of use assets obtained in exchange for material new lease obligations. Variable lease payments 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.

As of December 31, 2019, future minimum commitments under ASC 842 under the Company's property leases were as follows (in thousands):

| | | |
|-------------------------------------|----|---------------|
| Due in: | | |
| 2020 | \$ | 6,498 |
| 2021 | | 5,383 |
| 2022 | | 5,039 |
| 2023 | | 3,614 |
| 2024 | | 3,715 |
| Thereafter | | 18,871 |
| Total future minimum lease payments | | 43,120 |
| Less: Leases not yet commenced | \$ | (5,073) |
| Less: imputed interest | | (16,835) |
| Total operating lease payments | \$ | <u>21,212</u> |

As of December 31, 2018, future minimum commitments under ASC 840 under the company's leases were as follows (in thousands):

| | | |
|-------------------------------------|----|---------------|
| Due in: | | |
| 2019 | \$ | 3,303 |
| 2020 | | 4,910 |
| 2021 | | 4,135 |
| 2022 | | 3,921 |
| 2023 | | 2,844 |
| Thereafter | | 20,386 |
| Total future minimum lease payments | \$ | <u>39,499</u> |

8. Notes Payable

In May 2019, the Company entered into a senior term facilities agreement (the "Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), as agent, and additional lenders from time to time (together with MidCap Financial, the "Lenders"), to borrow up to \$75.0 million in term loans. To date, the Company has borrowed \$25.0 million under an initial term loan. The remaining \$50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a \$25.0 million term loan available no earlier than September 30, 2019 and no later

than December 31, 2020 upon submission of certain regulatory filings and evidence of the Company having \$100.0 million in cash and cash equivalent investments; and the third term loan being a \$25.0 million term loan available no earlier than July 1, 2020 and no later than September 30, 2021 upon certain regulatory approvals and evidence of the Company having \$125.0 million in cash and cash equivalent investments. As of December 31, 2019, the Company had met the criteria to draw down the second term loan of \$25.0 million.

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

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

As of December 31, 2019, notes payable consist of the following (in thousands):

| | December 31, | |
|--------------------------------------|------------------|-------------|
| | 2019 | 2018 |
| Notes payable, net of issuance costs | \$ 24,541 | \$ — |
| Accretion related to final payment | 158 | — |
| Notes payable, long term | <u>\$ 24,699</u> | <u>\$ —</u> |

As of December 31, 2019, the estimated future principal payments due are as follows (in thousands):

| | Aggregate Minimum Payments |
|---|----------------------------------|
| 2020 | \$ — |
| 2021 | 4,861 |
| 2022 | 8,333 |
| 2023 | 8,334 |
| 2024 | 4,597 |
| Thereafter | — |
| Total | <u>26,125</u> |
| Less unamortized portion of final payment | (967) |
| Less unamortized debt issuance costs | (459) |
| Notes payable, long term | <u>\$ 24,699</u> |

During the year ended December 31, 2019, the Company recognized \$1.5 million of interest expense related to the initial Term Loan. The effective annual interest rate as of December 31, 2019 on the outstanding debt under the Term Loan was approximately 10.5%.

9. Shareholders' Equity and Convertible Preferred Shares

Ordinary shares

As of December 31, 2019, and 2018, 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 December 31, 2019, and 2018, the Company has not declared any dividends.

As of December 31, 2019, and 2018, 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.

Initial Public Offering, Follow-on Public Offering and Corporate Reorganization

In November 2018, the Company completed its initial public offering ("IPO") of ADSs. In the IPO, the Company sold an aggregate of 16,103,572 ADSs representing the same number of ordinary shares at a public offering price of \$14.00 per ADS, including a partial exercise by the underwriters of their option to purchase additional ADSs. Net proceeds were \$205.5 million, after deducting underwriting discounts of \$15.8 million, and commissions and offering expenses paid by the Company of \$4.2 million.

In June 2019, the Company completed its follow-on public offering of ADSs. The Company sold an aggregate of 9,725,268 ADSs representing the same number of ordinary shares at a public offering price of \$14.25 per ADS, including a partial exercise by the underwriters of their option to purchase additional ADSs. Net proceeds were \$129.7 million, after deducting underwriting discounts of \$8.3 million, and commissions and offering expenses paid by the Company of \$0.6 million.

Immediately prior to the completion of the IPO, all outstanding convertible preferred shares of the Company were converted into their respective class of preferred shares on a one-for-0.8003 basis. All ordinary shares were consolidated on a one-for-0.8003 basis. Following completion of these steps, and immediately prior to the completion of the IPO, each share outstanding was re-designated as an ordinary share on a one-for-one basis. Accordingly, all share and per share amounts for all periods presented in the accompanying condensed consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect this reverse split. In addition, all share options for all periods presented have been adjusted retroactively to reflect this reverse split.

Additionally, as part of the corporate reorganization associated with the Company's IPO, each ordinary share with a nominal value of £0.00001 was redenominated as an ordinary share with a nominal value of £0.10. Accordingly, equity accounts for all periods presented in the condensed consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the effects of the redenomination of our ordinary shares.

Other ordinary share issuances

In November 2016, as amended in September 2018, the Company entered into a license and development agreement with Oxford BioMedica U.K. Limited ("Oxford BioMedica"). As consideration for the rights and licenses granted to the Company under the license and development agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica in December 2016. The Company also agreed to grant additional ordinary shares upon achievement of specified milestones. In November 2017, the first milestone was achieved, and the Company was obligated to issue an additional 150,826 shares. The shares issued in 2016 and 2017 were recorded based on their fair values at the time the agreement was executed of \$0.5 million and \$0.1 million, respectively. In August 2018, the terms of the arrangement were modified to extend milestone achievement dates under the agreement, and a second milestone was met, and the company issued an additional 150,826 shares. The shares issued in 2018 were recorded based on their fair value at the time the agreement was modified of \$1.4 million. The amounts were recorded to research and development expense in the years ended December 31, 2018, 2017, and 2016, respectively.

In February 2016, and amended in July 2017, the Company entered into a license agreement (the "UCLB/UCLA License Agreement") with UCL Business PLC ("UCLB"), which is the commercialization company of University College London, and The Regents of the University of California ("UCLA"), pursuant to which the Company issued nil, 1,224,094, and 3,441,290 ordinary shares in 2018, 2017 and 2016, respectively, to UCLB. The shares were recorded at their fair values as of the time the agreement was executed or modified, which was an aggregate of \$3.8 million. Amounts totaling \$1.7 million and \$2.1 million were recorded to research and development expense for the years ended December 31, 2017 and 2016, respectively.

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. Pursuant to these agreements, the Company issued 256,096 and 800,380 ordinary shares in 2017 and 2016, respectively. The share commitments were recorded to research and development expense based on their fair values as of the time the respective agreement was executed or modified. The amounts were \$1.4 million and \$0.5 million in 2017 and 2016, respectively.

As of December 31, 2019, and 2018, the Company had outstanding 96,923,729 and 85,865,557 ordinary shares, respectively.

10. Share-based Compensation

The Company maintains three 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”), and the 2018 Employee Share Purchase Plan (the “ESPP”). The board of directors has determined not to make any further awards under the 2016 plan following the Company’s IPO. On March 22, 2019, pursuant to the evergreen provisions in the 2018 Plan and the ESPP, the Company increased (i) the number of ordinary shares available for issuance under the 2018 Plan by 4,293,278, and (ii) the number of ordinary shares available for issuance under the ESPP by 858,656. As of December 31, 2019, 4,687,029 shares remained available for grant under the 2018 Plan, and 1,580,887 shares remained available for grant under the ESPP.

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

Options and option valuation

The assumptions used in the Black-Scholes option pricing model to determine the fair value of the share options granted to employees, non-employees, and directors during the year ended December 31, 2019, 2018, and 2017 were as follows:

| | Year Ended December 31, | | |
|--------------------------|-------------------------|--------------|---------------|
| | 2019 | 2018 | 2017 |
| Risk-free interest rate | 1.39 - 2.62% | 2.66 - 3.03% | 1.52 - 2.30% |
| Expected term (in years) | 5.50 - 6.08 | 5.00 - 6.08 | 6.08 |
| Expected volatility | 70.1 - 72.1% | 64.3 - 68.6% | 77.8% - 80.0% |
| Expected dividend rate | 0.00% | 0.00% | 0.00% |

The Company uses the simplified method as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term for options granted to employees and utilizes the contractual term for options granted to non-employees. The expected term is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. 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 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 Company accounts for forfeitures as they occur.

Options

The following table summarizes option activity under the plans for the year ended December 31, 2019 (in thousands, except share and per share amounts):

| | Shares | Weighted Average Exercise Price per Share | Weighted Average Remaining Contractual Life (Years) | Aggregate Intrinsic Value |
|---|-------------|---|---|---------------------------|
| Outstanding at December 31, 2018 | 10,203,432 | \$ 3.04 | 8.97 | \$ 129,551 |
| Granted | 4,681,282 | 13.57 | | |
| Exercised | (1,209,335) | 1.65 | | |
| Forfeited | (1,459,239) | 7.36 | | |
| Outstanding and expected to vest at December 31, 2019 | 12,216,140 | \$ 6.61 | 8.31 | \$ 91,133 |
| Exercisable, as of December 31, 2019 | 4,528,094 | \$ 3.59 | 7.72 | \$ 46,131 |

The weighted average exercise price of options granted to United Kingdom employees in 2018 was the nominal value of the underlying shares. The weighted average exercise price of options granted to United States employees in 2018 was \$5.74 per share.

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 2019, the total intrinsic value of share options exercised was \$17.2 million. During 2018 and 2017 the total intrinsic value of share options exercised was not material.

The weighted average grant date fair value of the options granted during the years ended December 31, 2019, 2018, and 2017 was \$8.67 per share, \$5.23 per share, and \$2.70 per share, respectively. All share options have 10-year terms.

Restricted Share Units

The Company has issued performance-based restricted share units ("RSUs") to certain executives and members of its senior management, with vesting linked to the achievement of three specific regulatory and research and development milestones and one market condition based upon the volume weighted-average price ("VWAP") of the Company's ADSs for a certain period. Upon achievement of any of the aforementioned milestones, one third of the RSU's will vest, and the award will become fully vested upon achievement of three of the four performance conditions.

The maximum aggregate total fair value of the outstanding performance based RSUs is \$10.1 million as of December 31, 2019. The fair value associated with the shares that could vest based on the market-based condition is being recognized as expense over an average derived service period of 1.3 years. The fair value associated with the performance-based conditions will be recognized when achievement of the milestones becomes probable, if at all. The Company determined that, as of December 31, 2019, none of the regulatory and research and development milestones were deemed probable.

The following table summarizes award activity for the year-end December 31, 2019:

| | Shares | Weighted Average Fair Value per Share |
|-------------------------------|----------|---------------------------------------|
| Unvested at December 31, 2018 | 219,922 | \$ 15.48 |
| Granted | 428,000 | 12.29 |
| Vested | — | |
| Forfeited | (91,500) | 12.13 |
| Unvested at December 31, 2019 | 556,422 | \$ 13.58 |

The amount of compensation cost recognized for the years ended December 31, 2019, 2018 and 2017 for the market condition associated with the performance based RSUs was \$1.2 million, \$0.1 million and nil, 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:

| | Year Ended December 31, | | |
|-------------------------------------|-------------------------|-----------------|-----------------|
| | 2019 | 2018 | 2017 |
| Research and development | \$ 7,425 | \$ 2,740 | \$ 615 |
| Selling, general and administrative | 11,999 | 4,026 | 404 |
| Total | <u>\$ 19,424</u> | <u>\$ 6,766</u> | <u>\$ 1,019</u> |

The Company had 7,688,046 unvested options outstanding as of December 31, 2019. As of December 31, 2019, total unrecognized compensation cost related to unvested stock option grants was approximately \$48.0 million. This amount is expected to be recognized over a weighted average period of approximately 2.6 years. As of December 31, 2019, the total unrecognized compensation cost related to performance based RSUs is a maximum of \$8.8 million, dependent upon achievement of milestones.

11. License and Research Arrangements

GSK asset purchase and license agreement

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

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

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations. Total consideration of £94.2 million (\$133.6 million at the acquisition date), which includes an upfront payment of £10.0 million (\$14.2 million at the acquisition date) and 12,455,252 convertible preferred shares of the Company issued to GSK at an aggregate value of £65.8 million (\$93.4 million at the acquisition date), a loss contract on the Strimvelis program valued at £12.9 million (\$18.4 million), an inventory purchase liability valued at £4.9 million (\$6.9 million) and transaction costs of £0.6 million (\$0.8 million). The Company allocated £94.2 million (\$133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development). The convertible preferred shares were converted to ordinary shares as part of our IPO in November 2018.

The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher (“PRV”) from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDT, the first of which GSK retained beneficial ownership over. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. For accounting purposes, as of December 31, 2019, the Company does not consider the attainment of a PRV from the United States Food and Drug Administration to be probable.

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as the Company’s OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a

liability associated with the loss contract of £12.9 million (\$18.4 million at the acquisition date) associated with the loss expected due to this obligation. This liability is being amortized over the remaining period of expected sales of Strimvelis as a credit to research and development expenses (see Note 2).

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and the Company-developed product candidate, OTL-101. The Company will also pay tiered royalty rates at a percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at a percentage from the high single-digits to low double-digit for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

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

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

Telethon-OSR research and development collaboration and license agreements

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

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement. The Company may pay up to an aggregate of approximately €31.0 million (\$34.8 million at December 31, 2019) in milestone payments upon achievement of certain product development milestones for the program.

In May 2019, the Company entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Company an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's *ex vivo* autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I ("MPS-I"), including the Hurler variant. Under the terms of the agreement, Telethon-OSR received €15.0 million 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 make milestone payments contingent upon certain development, regulatory and commercial milestones are achieved. Additionally, the Company will be required to pay Telethon a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

UCLB/UCLA License Agreement

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

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

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

The Company recorded \$0.1 million of research and development costs in respect of the UCLB/UCLA license agreement, which comprise the upfront payments, issuance of ordinary shares and payments for clinical data, for each of the years ended December 31, 2019, 2018 and 2017, respectively.

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 September 2018, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors to the Company (“Oxford BioMedica Agreement”). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and third milestones were achieved, and the Company issued 150,826 ordinary shares. No milestones were met during the year ended December 31, 2019.

The Company recorded \$0.5 million to research and development expense upon execution of the Oxford BioMedica Agreement in 2016 and \$0.1 million upon achievement of the first development milestone in 2017. The Company recorded \$1.4 million upon achievement of the second and third development milestones in 2018. The expense recognized in 2016 and 2017 was determined based on the ordinary shares’ fair value as of the time the agreement was executed. The expense recognized in 2018 was determined based on the ordinary shares’ fair value as of the time the agreement was modified in September 2018. There was no expense recorded associated with the license agreement in year ended December 31, 2019 as no milestones were met or became probable during the period.

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

UCLA/CIRM research agreement

In January 2017, the Company and UCLA executed a subcontract agreement (“UCLA Research Agreement”), whereby the Company would provide UCLA certain research and development services related to autologous *ex vivo* lentiviral gene therapy in ADA-SCID as part of UCLA’s existing ADA-SCID research program that is being funded by the California Institute for Regenerative Medicine (“CIRM”). The original amount of total reimbursement the Company could have received under the UCLA Research Agreement was \$10.4 million. Through June 30, 2018, the Company received and recognized \$7.3 million from this agreement. In July 2018, a transfer of the sponsorship took place and the Company became the awardee under the program funded by CIRM, and the Company received an award that superseded the previous award noted above. The total reimbursement the Company may receive under the new award is \$8.5 million, of which the Company is obligated to reimburse UCLA for up to \$5.5 million for research activities, subject to achievement of certain milestones outlined in the CIRM grant. Reimbursement may be received from CIRM during the period from January 2017 to December 2021. Under the terms of the CIRM grants, the Company is obligated to pay a low single-digit percentage royalty on net sales of CIRM-funded product candidates or CIRM-funded technology. The Company has the option to decline any and all amounts awarded by CIRM. As an alternative to revenue sharing, the Company has the option to elect to convert the award to a loan, in which case the full loan amount becomes payable within 10 days of election. No such election has been made as of the date. The reimbursements are recognized as a reduction in research and development expense for research activities that

have taken place. In the event the reimbursement is received in advance of research activities, it is recognized within other liabilities. The Company accrues the sales-based royalties associated with CIRM-funded products when payment becomes probable. To date, no royalties have been accrued.

For the years ended December 31, 2019, 2018 and 2017, the Company recorded nil, \$3.0 million, and \$5.0 million, respectively, as a reduction of research and development expenses related to the UCLA Research Agreements. As of December 31, 2019, and 2018, the Company recorded nil and \$1.6 million in accrued expenses for amounts which it is obligated to reimburse to UCLA under the July 2018 grant, respectively.

12. Income Taxes

The components of income (loss) from operations before income taxes for the years ended December 31, 2019, 2018, and 2017 are as follows (in thousands):

| | December 31, | | |
|-------------------|---------------------|---------------------|--------------------|
| | 2019 | 2018 | 2017 |
| U.K. | \$ (173,118) | \$ (230,543) | \$ (39,422) |
| Non-U.K. | 7,456 | 1,018 | (269) |
| Loss before taxes | <u>\$ (165,662)</u> | <u>\$ (229,525)</u> | <u>\$ (39,691)</u> |

The (benefit from) provision for income taxes for the years ended December 31, 2019, 2018, and 2017 are as follows (in thousands):

| | December 31, | | |
|--|-------------------|---------------|--------------|
| | 2019 | 2018 | 2017 |
| Current (benefit) provision | | | |
| Federal—United States | \$ 888 | \$ 607 | \$ — |
| State—United States | (275) | 444 | 16 |
| United Kingdom | — | — | — |
| Other | 89 | — | — |
| Total current (benefit) provision | 702 | 1,051 | 16 |
| Deferred (benefit) provision | | | |
| Federal—United States | (2,820) | (31) | — |
| State—United States | (122) | (50) | 37 |
| United Kingdom | — | — | — |
| Total deferred (benefit) provision | (2,942) | (81) | 37 |
| Total (benefit) provision for income taxes | <u>\$ (2,240)</u> | <u>\$ 970</u> | <u>\$ 53</u> |

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

| | December 31, | | |
|--|-------------------|---------------|--------------|
| | 2019 | 2018 | 2017 |
| Income taxes at United Kingdom statutory rate | \$ (31,475) | \$ (43,526) | \$ (7,640) |
| Change in valuation allowance | 16,507 | 43,562 | 7,827 |
| Reduction in research expense for credits granted | 9,787 | — | — |
| Change in tax rates | 8,109 | — | — |
| Tax credits | (3,372) | — | (286) |
| U.S. Deduction for foreign derived intangible income | (2,058) | — | — |
| Permanent differences | 344 | 293 | 115 |
| U.S. state income taxes | (238) | 370 | 41 |
| Foreign rate differential | 156 | 20 | (40) |
| Impact of United States tax reform | — | 159 | 36 |
| Other | — | 92 | — |
| Total (benefit) provision for income taxes | <u>\$ (2,240)</u> | <u>\$ 970</u> | <u>\$ 53</u> |

The Company's income tax (benefit) expense for the year ended December 31, 2019 compared to the year ended December 31, 2018 increased primarily related to benefits associated with its U.S. federal research and development tax credits and U.S. foreign derived intangibles income deduction ("FDII").

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, 2019 and 2018 (in thousands):

| | December 31, | |
|--|-----------------|---------------|
| | 2019 | 2018 |
| Deferred tax assets | | |
| Net operating loss carryforwards | \$ 45,358 | \$ 29,436 |
| Amortization | 21,741 | 19,451 |
| Research and development credits | 1,244 | — |
| Share-based compensation | 3,604 | 1,297 |
| Accruals | 1,286 | 184 |
| Lease Liability | 4,406 | — |
| Other | 1 | 1,946 |
| Total deferred tax assets | 77,640 | 52,314 |
| Valuation allowance | (70,153) | (51,281) |
| Net deferred tax assets | 7,487 | 1,033 |
| Deferred tax liabilities | | |
| Operating lease right of use assets | (3,975) | — |
| Depreciation | (528) | (991) |
| Other non-current liabilities (net deferred tax assets and liabilities) | \$ 2,984 | \$ 42 |

As of December 31, 2019 and 2018, the Company had cumulative U.K. net operating loss carryforwards of approximately \$266.8 million and \$155.2 million, respectively. Unsurrendered U.K. losses may be carried forward indefinitely, subject to numerous utilization criteria and restrictions and are fully offset by a valuation allowance.

For the year ended December 31, 2019, the Company had cumulative U.S. federal general business and U.S. state research and development tax credit carryforwards of approximately \$0.1 million and \$1.4 million, respectively, available to reduce future U.S. tax liabilities. The U.S. federal general business tax credits will expire at various dates through 2039. The U.S. state tax credit carryforwards can be carried forward indefinitely and are fully offset by a valuation allowance.

The U.S. tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax credits that can be utilized annually to offset future U.S. tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has completed several financings since its inception that it believes may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code.

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

As of each reporting date, we consider new evidence, both positive and negative, that could impact our view with regard to future realization of our deferred tax assets. In the fourth quarter of 2019, 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, 2019 and 2018, respectively.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2019, 2018, and 2017 related primarily to the increase in U.K. net operating loss carryforwards and U.K. amortization of intangible assets were as follows (in thousands):

| | December 31, | | |
|---|--------------------|--------------------|--------------------|
| | 2019 | 2018 | 2017 |
| Valuation allowance as of beginning of year | \$ (51,281) | \$ (11,882) | \$ (3,503) |
| Decreases recorded as benefit to income tax provision | — | 604 | — |
| Increases recorded to income tax provision | (16,507) | (44,166) | (7,827) |
| Effect of foreign currency translation | (2,365) | 4,163 | (552) |
| Valuation allowance as of end of year | <u>\$ (70,153)</u> | <u>\$ (51,281)</u> | <u>\$ (11,882)</u> |

The Company applies the authoritative guidance on accounting for and disclosure of uncertainty in tax positions, which requires the Company to determine whether a tax position of the Company is more likely than not to be sustained upon examination, including resolution of any related appeals or 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, 2019 and 2018.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense when in a taxable income position. As of December 31, 2019 and 2018, 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 U.K., the U.S., and various foreign jurisdictions. Generally, the tax years 2016 through 2018 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.

13. Net Loss Per Share

The following table sets forth the computation of basic and diluted net loss per share (in thousands, except share and per share amounts):

| | Year Ended December 31 | | |
|---|------------------------|-------------------|------------------|
| | 2019 | 2018 | 2017 |
| Net loss attributable to ordinary shareholders | \$ (163,422) | \$ (230,495) | \$ (39,744) |
| Weighted average ordinary shares outstanding, basic and diluted | 93,240,355 | 22,559,389 | 8,872,768 |
| Net loss per share attributable to ordinary shareholders, basic and diluted | <u>\$ (1.75)</u> | <u>\$ (10.22)</u> | <u>\$ (4.48)</u> |

Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all shares convertible into ordinary shares outstanding would have been anti-dilutive.

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

| | December 31, | | |
|--|-------------------|------------------|-------------------|
| | 2019 | 2018 | 2017 |
| Convertible preferred shares | — | — | 33,277,678 |
| Share options | 10,056,864 | 9,179,247 | 3,612,288 |
| Unvested shares from share plan and consulting agreement | 751,496 | 219,922 | — |
| | <u>10,808,360</u> | <u>9,399,169</u> | <u>36,889,966</u> |

14. Commitments and Contingencies

Commitment with contract manufacturing organization

The Company has entered into agreements with contract manufacturing organizations relating to the provision of manufacturing services and purchase of clinical material to be used in clinical trials that include minimum purchase commitments. As of December 31, 2019, and December 31, 2018, there was nil and \$0.8 million included within prepayments relates to prepaid instalments against these minimum commitments. As of December 31, 2019, the Company is committed to make further payments totaling \$9.1 million between January 2020 and July 2022.

Other funding commitments

The Company has entered into several license agreements (Note 11). In connection with these agreements the Company is required to make milestone payments and annual license maintenance payments not met at December 31, 2019 and 2018 or royalties on future sales of specified products. The Company determined that no milestone payments were probable other than those already accrued as of December 31, 2019.

Consulting Agreement

In December 2019, the Company entered into a consulting agreement with non-employee advisor whereby the Company is obligated to make cash payments of \$0.1 million per year and to issue up to 91,034 ordinary shares, which vest annually over a four year period, and 92,035 ordinary shares upon attainment of certain clinical development and regulatory milestones. As of December 31, 2019, the Company recorded immaterial research and development expense associated with the share-based awards with service conditions. No expense was recorded associated with the performance-based conditions.

Legal proceedings

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

15. 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 five percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid \$1.3 million, \$0.6 million, and \$0.2 million in matching contributions for the years ended December 31, 2019, 2018 and 2017, respectively.

16. Related-party Transactions

GSK

In April 2018, the Company completed the GSK Agreement with subsidiaries of GSK (See Note 11). As consideration under the agreement the Company paid an upfront fee of \$14.2 million, purchased inventory of \$6.9 million, paid \$0.8 million in transaction costs, and issued 12,455,252 convertible preferred shares valued at \$93.4 million. Additionally, as part of the GSK Agreement, the Company obtained, and is responsible for maintaining the commercial availability of Strimvelis. The Company recorded a loss provision of \$18.4 million associated with the agreement, as the costs to maintain Strimvelis are

expected to significantly exceed revenues. The issuance of the convertible preferred shares made GSK a principal shareholder in the Company.

In 2019, the Company made \$7.2 million in payments to settle accounts payable due to GSK associated with the TSA and royalties associated with sales of Strimvelis incurred during 2018. Additionally, during 2019, the Company made a \$3.6 million payment associated with the inventory purchase liability incurred upon entering into the agreement, and \$0.1 million in royalties associated with Strimvelis sales during the year. In 2018 the Company paid \$14.0 million in pass-through research and development and royalty costs with GSK associated with the TSA. As of December 31, 2019, and 2018, the Company had inventory purchase liability in accrued research and development expenses of \$3.3 million and \$6.2 million, respectively.

17. Subsequent events

COVID-19

Since December 31, 2019, a novel strain of coronavirus, now referred to as COVID-19 has continued to spread globally, has been declared a pandemic by the World Health Organization and has spread to over 100 countries, including the United States and United Kingdom. The impact of this pandemic has been and will likely continue to be extensive in many aspects of society, which has resulted in and will likely continue to result in significant disruptions to the global economy, as well as businesses and capital markets around the world.

The Company is subject to risks associated with the COVID-19 pandemic. In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy, have placed significant restrictions on travel. Limitations on travel and other social distancing measures may have an effect on our clinical activities and regulatory timelines. Travel and stay-at-home orders could adversely affect our contract manufacturers and third-party logistics providers. Shelter-in-place and stay-at-home orders in California has caused the Company to temporarily suspend construction activities on our planned manufacturing facility in Fremont, California. Commercial activity associated with our EMA-approved gene therapy for ADA-SCID, Strimvelis®, has been postponed by the treatment site and scheduled patients are continuing to receive enzyme replacement therapy until treatment with Strimvelis can occur. Any prolonged material disruptions to the Company's employees, suppliers, contract manufacturers, vendors, or patients could impact our operating results and could lead to impairments. The Company's ability to access the capital markets could be impacted if disruptions in the capital markets continue.

18. Selected Quarterly Financial Information (unaudited)

The following table summarizes the unaudited quarterly financial data for the last two fiscal years (in thousands):

| | 2019 | | | | |
|--|---------------|--------------------|---------------|----------------|------------|
| | First Quarter | Second Quarter (1) | Third Quarter | Fourth Quarter | Full year |
| Total revenues | \$ - | \$ - | \$ 1,918 | \$ 595 | \$ 2,513 |
| Total costs and operating expenses | 28,283 | 54,152 | 43,330 | 49,621 | 175,386 |
| Loss from operations | (28,283) | (54,152) | (41,412) | (49,026) | (172,873) |
| Net loss attributable to ordinary shareholders | (30,739) | (50,530) | (36,737) | (45,416) | (163,422) |
| Weighted average ordinary shares outstanding - basic and diluted | 87,010,596 | 89,712,916 | 97,817,847 | 98,243,915 | 93,240,355 |
| Earnings per share | \$ (0.35) | \$ (0.56) | \$ (0.38) | \$ (0.46) | \$ (1.75) |
| | 2018 | | | | |
| | First Quarter | Second Quarter (2) | Third Quarter | Fourth Quarter | Full year |
| Total revenues | \$ - | \$ - | \$ 1,387 | \$ 689 | \$ 2,076 |
| Total costs and operating expenses | 13,698 | 158,412 | 35,477 | 29,520 | 237,107 |
| Loss from operations | (13,698) | (158,412) | (34,090) | (28,831) | (235,031) |
| Net loss attributable to ordinary shareholders | (15,311) | (156,233) | (33,888) | (25,063) | (230,495) |
| Weighted average ordinary shares outstanding - basic and diluted | 9,983,754 | 10,115,335 | 10,294,498 | 59,435,325 | 22,559,389 |
| Earnings per share | \$ (1.53) | \$ (15.45) | \$ (3.29) | \$ (0.42) | \$ (10.22) |

- (1) The increase in total costs and operating expenses in the second quarter of 2019 is due to the \$17.2 million in-process research and development charge resulting from the licensing of a clinical stage development program for the treatment of MPS-I from Telethon-OSR (see Note 11).
- (2) The significant increase in total costs and operating expenses in the second quarter of 2018 is due to the \$133.6 million in-process research and development charge resulting from the GSK Agreement (see Note 11).

As disclosed in Note 2, the Company adopted ASC 842 on December 31, 2019, with an effective date of January 1, 2019. In previously issued interim financial statements within the nine months ended September 30, 2019, the Company applied the guidance in ASC 840 for its leases. In connection with the adoption of ASC 842, there are no changes required to the amounts presented in the previously issued 2019 interim condensed consolidated statements of operations and comprehensive loss.

