UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 31, 2021

OR

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

For the transition period from to

Commission File Number: 001-38722

ORCHARD THERAPEUTICS PLC

(Exact Name of Registrant as Specified in its Charter)

England and Wales	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
108 Cannon Street	
London, United Kingdom	**EC4N 6EU**
(Address of principal executive offices)	**(Zip Code)**

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

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

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

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

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

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

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

Indicate by check mark whether the registrant has filed all documents and reports required to be filed by Sections 12, 13 or 15(d) of the Securities Exchange Act of 1934 subsequent to the distribution of securities under a plan confirmed by a court. Yes ☒ No ☐

As of May 4, 2021, the registrant had 123,769,373 voting and non-voting ordinary shares, nominal value £0.10 per share, outstanding.

Summary of the Material Risks Associated with Our Business

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

- We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.
- We will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.
- Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.
- The results from our clinical trials for OTL-200 for metachromatic leukodystrophy, or MLD, OTL-103 for Wiskott Aldrich syndrome, or WAS, and for any of our other product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. Before we submit our product candidates for marketing approval, the U.S. Food and Drug Administration, or FDA, and/or the European Medicines Agency, or EMA, may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.
- Interim data and ad hoc analyses are preliminary in nature. Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.
- Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience and we rely on third party manufacturers that are often our single source of supply. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial products or our product candidates or otherwise harm our business.
- Libmeldy™, Strimvelis® and our product candidates and the process for administering Libmeldy, Strimvelis and our product candidates may cause serious or undesirable side effects or adverse events or have other properties that could delay or prevent regulatory approval, limit commercial potential or result in significant negative consequences for our company.
- We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.
- If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market, sell and gain reimbursement for Libmeldy and our product candidates that may be approved, we may not be successful in commercializing Libmeldy or our product candidates if and when approved, and we may be unable to generate product revenue.
- If the size and value of the market opportunities for our commercial products or product candidates are smaller than our estimates, or if we have difficulty in finding patients that meet eligibility requirements for Libmeldy, Strimvelis or any of our product candidates, if approved, our product revenues may be adversely affected and our business may suffer.
- We face significant competition in our industry and there can be no assurance that our commercial products or our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.
- Business interruptions resulting from the COVID-19 pandemic or similar public health crises have caused and may cause or continue to cause a disruption to the development of our product candidates and adversely impact our business.
- We may not be able to protect our intellectual property rights throughout the world.
- We may become subject to claims that we are infringing certain third-party patents, for example, patents relating to lentiviral vectors, or other third-party intellectual property rights, any of which may prevent or delay our development and commercialization efforts and have a material adverse effect on our business.
- We have entered into collaborations with third parties to develop or commercialize product candidates and we may continue to do so in the future. If these collaborations are not successful, our business could be adversely affected.
- The market price of our ADSs may be highly volatile and may fluctuate due to factors beyond our control.

The summary risk factors described above should be read together with the text of the full risk factors below, in the section entitled “Risk Factors” in Part I, Item 1.A. and the other information set forth in this Quarterly Report on Form 10-Q for the period ended March 31, 2021, as well as in other documents that we file with the U.S. Securities and Exchange Commission. The risks summarized above or described in full below are not the only risks that we face. Additional risks and uncertainties not precisely known to us, or that we currently deem to be immaterial may also materially adversely affect our business, financial condition, results of operations and future growth prospects.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 10-Q, or 10-Q, 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 10-Q are based upon information available to our management as of the date of this 10-Q, 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 10-Q 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 market opportunity for and size of the patient populations for Libmeldy (OTL-200) and our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial products, product candidates and technology;
- our plans and ability to build out our commercial infrastructure and successfully identify eligible patients, launch, market, and sell Libmeldy in Europe and any current and future product candidates for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of Libmeldy, Strimvelis, and any of our product candidates, if approved, including reimbursement for patients treated in a country where they are not resident;
- the adequacy, scalability and commercial viability of our manufacturing capacity, methods and processes, including those of our manufacturing partners, and plans for future development;
- the rate and degree of market acceptance and clinical utility of our commercial products and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- the impact of the COVID-19 global pandemic on our business operations, including clinical trials, regulatory strategy, and the operations of our third-party manufacturers, suppliers, and partners;
- 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 products and product candidates;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our ability to attract and retain qualified employees and key personnel;
- our ability to contract with third party suppliers, clinical sites and manufacturers and their ability to perform adequately;
- our projected financial condition, including the sufficiency of our cash, cash equivalents and investments to fund operations in future periods and future liquidity, working capital and capital requirements; and
- other risks and uncertainties, including those listed under the caption “Item 1A. Risk Factors” in this 10-Q.

You should refer to the section titled “Item 1A. Risk Factors” in this 10-Q 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 10-Q 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 10-Q and the documents that we reference in this 10-Q and have filed as exhibits to this 10-Q 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—FINANCIAL INFORMATION

Item 1. Financial Statements.

ORCHARD THERAPEUTICS PLC
Condensed Consolidated Balance Sheets
(In thousands, except per share amounts)
(unaudited)

	March 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 78,883	$ 55,135
Marketable securities	219,543	136,813
Trade receivables	—	878
Prepaid expenses and other current assets	12,504	13,365
Research and development tax credit receivable, current	17,493	17,344
Total current assets	328,423	223,535
Non-current assets:		
Operating lease right-of-use-assets	28,700	29,815
Property and equipment, net	4,591	4,781
Research and development tax credit receivable, net of current portion	3,552	—
Restricted cash	4,266	4,266
Other assets	19,581	18,540
Total assets	$ 389,113	$ 280,937
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 7,905	$ 8,823
Accrued expenses and other current liabilities	25,672	28,943
Operating lease liabilities	7,964	8,934
Notes payable current	6,944	4,861
Total current liabilities	48,485	51,561
Notes payable, long term	18,208	20,204
Operating lease liabilities, net of current portion	20,847	24,168
Other long-term liabilities	5,993	6,570
Total liabilities	93,533	102,503
Commitments and contingencies (see Note 12)		
Shareholders' equity:		
Ordinary shares, £0.10 nominal value; 120,549,163 and 98,283,603 ordinary shares issued and outstanding at March 31, 2021 and December 31, 2020, respectively; 3,215,434 and nil non-voting ordinary shares issued and outstanding at March 31, 2021 and December 31, 2020, respectively	15,995	12,507
Additional paid-in capital	920,211	771,194
Accumulated other comprehensive income	196	373
Accumulated deficit	(640,822)	(605,640)
Total shareholders' equity	295,580	178,434
Total liabilities and shareholders' equity	$ 389,113	$ 280,937

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share amounts)
(unaudited)

	Three Months Ended March 31,	
	2021	2020
Product sales, net	$ —	$ —
Costs and operating expenses:		
Research and development	21,035	24,836
Selling, general and administrative	14,051	20,145
Total costs and operating expenses	35,086	44,981
Loss from operations	(35,086)	(44,981)
Other income (expense):		
Interest income	171	1,480
Interest expense	(538)	(613)
Other income (expense), net	1,358	(6,790)
Total other income (expense), net	991	(5,923)
Net loss before income tax	(34,095)	(50,904)
Income tax (expense) benefit	(1,087)	335
Net loss	(35,182)	(50,569)
Other comprehensive (loss) income:		
Foreign currency translation adjustment	(64)	6,034
Unrealized loss on marketable securities	(113)	(1,021)
Total other comprehensive (loss) income:	(177)	5,013
Total comprehensive loss	$ (35,359)	$ (45,556)
Net loss per share, basic and diluted	$ (0.31)	$ (0.51)
Weighted average ordinary shares outstanding, basic and diluted	114,829,272	98,713,126

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements of Cash Flows
(In thousands)
(unaudited)

	Three Months Ended March 31,	
	2021	**2020**
Cash flows from operating activities:		
Net loss	$ (35,182)	$ (50,569)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	495	482
Non-cash share-based compensation	6,268	9,479
Amortization of Strimvelis loss provision	(446)	(1,691)
Other non-cash adjustments	2,968	6,537
Changes in operating assets and liabilities:		
Trade receivables	887	670
Research and development tax credit receivable	(3,554)	(3,385)
Prepaid expenses, other current assets and other assets	1,399	(2,500)
Operating leases, right-of-use assets	1,252	1,025
Accounts payable, accrued expenses and other current liabilities	(8,905)	(8,903)
Operating lease liabilities	(4,424)	(1,047)
Net cash used in operating activities	(39,242)	(49,902)
Cash flows from investing activities:		
Proceeds from sales and maturities of marketable securities	47,200	68,143
Purchases of marketable securities	(130,387)	—
Payment of construction deposit	—	(10,000)
Purchases of property and equipment	(339)	(1,329)
Net cash (used in) provided by investing activities	(83,526)	56,814
Cash flows from financing activities:		
Proceeds from equity plans	2,822	1,438
Taxes paid on net settlement of equity plan issuances	(296)	—
Proceeds from the issuance of ordinary shares in private placement	150,000	—
Payment of placement agent fees and offering costs	(6,092)	—
Net cash provided by financing activities	146,434	1,438
Effect of exchange rate changes on cash, cash equivalents, and restricted cash	82	(303)
Net increase in cash, cash equivalents and restricted cash	23,748	8,047
Cash, cash equivalents, and restricted cash, beginning of period	59,401	23,317
Cash, cash equivalents, and restricted cash, end of period	$ 83,149	$ 31,364
Supplemental disclosure of non-cash activities		
Property and equipment and intangible assets included in accounts payable and accrued expenses	$ 4,834	$ 382
Offering costs included in accounts payable and accrued expenses	198	—
Lease assets obtained in exchange for new operating lease liabilities	—	3,752
Supplemental disclosure of cash flow information:		
Cash paid for interest	482	485

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements of Shareholders' (Deficit) Equity

(In thousands, except share and per share amounts)

(unaudited)

	Ordinary Shares		Additional Paid-In Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total
	Shares	Amount				
Balance at December 31, 2019	96,923,729	$ 12,331	$ 738,481	$ 2,042	$ (453,661)	$ 299,193
Share-based compensation expense	—	—	9,479	—	—	9,479
Exercise of share options	230,836	30	1,408	—	—	1,438
Foreign currency translation	—	—	—	6,034	—	6,034
Unrealized loss on available for sale debt securities	—	—	—	(1,021)	—	(1,021)
Net loss	—	—	—	—	(50,569)	(50,569)
Balance at March 31, 2020	97,154,565	$ 12,361	$ 749,368	$ 7,055	$ (504,230)	$ 264,554
Balance at December 31, 2020	98,283,603	$ 12,507	$ 771,194	$ 373	$ (605,640)	$ 178,434
Share-based compensation expense	—	—	6,268	—	—	6,268
Exercise of share options	1,319,493	172	2,650	—	—	2,822
Vesting of restricted stock units, net of shares withheld for taxes	45,746	6	(302)	—	—	(296)
Sale of ordinary shares and non-voting ordinary shares, net of issuance costs of $6,290	24,115,755	3,310	140,401	—	—	143,711
Foreign currency translation	—	—	—	(64)	—	(64)
Unrealized loss on available for sale debt securities	—	—	—	(113)	—	(113)
Net loss	—	—	—	—	(35,182)	(35,182)
Balance at March 31, 2021	123,764,597	$ 15,995	$ 920,211	$ 196	$ (640,822)	$ 295,580

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

1. Nature of the Business

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

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

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

On February 9, 2021, the Company issued and sold (i) 20,900,321 ordinary shares, nominal value £0.10 per share, at a purchase price of $6.22 per share (the "Purchase Price"), which was the closing sale price of the Company's ADSs on the Nasdaq Global Select Market on February 4, 2021, and (ii) 3,215,434 non-voting ordinary shares, nominal value £0.10 per share, at the Purchase Price (together (i) and (ii) the "Private Placement"). The Private Placement resulted in net proceeds to the Company of $143.7 million after deducting placement agent fees of $6.0 million and other issuance costs of $0.3 million. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement entered into between the Company and the purchasers named therein on February 4, 2021.

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

Through March 31, 2021, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares, ADSs in the Company's initial public offering (the "IPO") and follow-on offering, ordinary shares in the Private Placement, proceeds from share issuances from employee equity plans, receipts from the United Kingdom ("UK") research and development tax credit, and reimbursements from our research agreements with the University of California ("UCLA") and the California Institute of Regenerative Medicine ("CIRM"). The Company has incurred recurring losses since its inception. As of March 31, 2021, the Company had an accumulated deficit of $640.8 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 March 31, 2021 of $298.4 million will be sufficient to fund its operations and capital expenditure requirements for at least the next twelve months.

The Company will seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into collaborations or other arrangements. The terms of any financing may adversely affect the holdings or the rights of the Company's shareholders. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

2. Basis of Presentation and Summary of Significant Accounting Policies

Basis of presentation

The condensed consolidated interim financial statements of the Company are unaudited and have been prepared in accordance with generally accepted accounting principles in the United States of America ("U.S. GAAP") for interim financial reporting and in accordance with Regulation S-X, Rule 10-01. Accordingly, they do not include all of the information and footnotes required by U.S. GAAP for complete financial statements. Any reference in these notes to applicable guidance is meant to refer to the authoritative U.S. GAAP as found in the Accounting Standards Codification ("ASC"), and Accounting Standards Update ("ASU"), of the Financial Accounting Standards Board ("FASB"). All intercompany accounts and transactions between the Company and its subsidiaries have been eliminated upon consolidation.

The accompanying unaudited condensed consolidated interim financial statements should be read in conjunction with the audited consolidated financial statements and accompanying notes included in the Company's Annual Report on Form 10-K filed with the SEC on March 2, 2021 (the "Annual Report"). The condensed consolidated balance sheet as of December 31, 2020 was derived from audited consolidated financial statements included in the Company's Annual Report but does not include all disclosures required by U.S. GAAP.

Certain information and footnote disclosures normally included in financial statements prepared in accordance with U.S. GAAP have been condensed or omitted from these interim financial statements. However, these interim financial statements include all adjustments, consisting only of normal recurring adjustments, which are, in the opinion of the Company's management, necessary to fairly state the results of the interim period. The interim results are not necessarily indicative of results to be expected for the full year.

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

Use of estimates

The preparation of condensed 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 condensed consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these condensed consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the research and development tax credit receivable, share-based compensation, operating lease assets and liabilities, and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. The future developments of the COVID-19 pandemic may also directly or indirectly impact the Company's business, including impacts due to quarantines, border closures, increased border controls, travel restrictions, shelter-in-place orders and shutdowns, business closures, cancellations of public gatherings and other measures. Actual results could differ from the Company's estimates.

Foreign currency

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. dollar are translated into U.S. dollars using period-end exchange rates for assets and liabilities, historical exchange rates for shareholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in shareholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations. The Company recorded realized and unrealized foreign currency transaction gains of $1.4 million and losses of $6.8 million for the three months ended March 31, 2021 and 2020, respectively, which is included in other income (expense), net in the condensed consolidated statements of operations and comprehensive loss.

Cash and cash equivalents

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

Marketable debt securities

Marketable securities consist of investments with original maturities greater than ninety days at the date of acquisition. The Company has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment

portfolio of investments as available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices or other observable inputs. Unrealized gains and losses are recorded as a component of other comprehensive income (loss). Realized gains and losses are determined on a specific identification basis and are included in other income (loss). Amortization and accretion of discounts and premiums is also recorded in other income (loss).

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

United Kingdom research and development tax credit

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

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

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

The Company recognizes credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expense in the condensed consolidated statement of operations and comprehensive loss. The following table below outlines the changes to the research and development tax credit receivable, including amounts recognized as an offset to research and development expense during the period:

	Three Months Ended March 31,	
	2021	2020
Balance at beginning of period	$ 17,344	$ 28,644
Recognition of credit claims as offset to research and development expense	3,554	3,417
(Receipt) of credit claims	—	—
Foreign currency translation	147	(1,850)
Balance at end of period	$ 21,045	$ 30,211

As of March 31, 2021, the Company's tax incentive receivable from the UK government was $21.1 million, of which $17.5 million was classified as current and $3.6 million was classified as long-term. As of December 31, 2020, the Company's tax incentive receivable from the UK government was $17.3 million, all of which was classified as current.

Restricted cash and construction deposits

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

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

	March 31, 2021	December 31, 2020
Cash and cash equivalents	$ 78,883	$ 55,135
Restricted cash	4,266	4,266
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 83,149	$ 59,401

The Company has $8.1 million in an escrow account associated with construction on the Fremont facility, for which the Company has ceased construction and build-out and subleased to a third-party. Subject to the terms of the lease and reduction provisions, this amount may be returned to the Company upon qualifying construction expenditure or will be returned in late 2022 (the "Sunset Date") to the extent construction expenses have not been incurred. The Company deposited $10.0 million into the account in the first quarter of 2020 and has received $1.9 million in receipts from the escrow funds for costs incurred to date. Of the $8.1 million remaining in the escrow account, $1.6 million is classified within prepaid expenses and other current assets and $6.5 million is classified within other assets on the condensed consolidated balance sheet based on the timing of when the Company expects funds to be returned from the escrow agent. Future receipts from the escrow deposit will be dependent upon the timing of the subtenant construction spend through the Sunset Date.

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

Comprehensive loss

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

Leases

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

As the Company's leases do not provide an implicit rate, the Company utilized the appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term as the lease an amount equal to the lease payments in a similar economic environment. The Company estimated the incremental borrowing rate based on the Company's currently outstanding credit facility as inputs to the analysis to calculate a spread, adjusted for factors that reflect the profile of secured borrowing over the expected term of the lease.

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

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

Strimvelis loss provision

As part of the GSK transaction (as detailed in Note 10), the Company is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company initially recorded a liability associated with the loss contract of $18.4 million in 2018. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with 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 reduction in research and development expense. The Company has made an estimate of the expected future losses associated with Strimvelis and adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of the future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for updates to estimates of potential future losses. The Company will continue to evaluate its future estimates for amortization of the Strimvelis loss provision. The following table below outlines the changes to the Strimvelis loss provision for the periods ended March 31, 2021 and 2020:

	Three Months Ended March 31,	
	2021	2020
Balance at beginning of period	$ 4,482	$ 6,790
Amortization of loss provision	(446)	(1,691)
Foreign currency translation	40	(348)
Balance at end of period	$ 4,076	$ 4,751

Of the balance as of March 31, 2021 noted in the table above, $1.1 million is classified as current, and $3.0 million is classified as non-current.

Net loss per share

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

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

	Three Months Ended March 31,	
	2021	2020
Share options	12,935,554	12,688,361
Unvested performance-based restricted share units	717,167	511,324
	13,652,721	13,199,685

Recent Accounting Pronouncements

Recently adopted accounting pronouncements

In December 2019, the FASB issued ASU No. 2019-12, *Simplifying the Accounting for Income Taxes (Topic 740)*, which removes certain exceptions to the general principles in Topic 740 – *Income Taxes* and improves consistent application of and simplifies GAAP for other areas of Topic 740 by clarifying and amending existing guidance. This ASU is effective for the Company beginning January 1, 2021 and did not have a material impact on our condensed consolidated financial statements.

3. Fair Value Measurements and Marketable Debt Securities

The following tables present information about the Company's financial assets that have been measured at fair value as of March 31, 2021 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 three months ended March 31, 2021, there were no transfers between Level 1 and Level 2 financial assets.

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

	Fair Value Measurements at March 31, 2021 Using:			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 26,091	$ —	$ —	$ 26,091
Corporate bonds	—	$ 5,174	—	5,174
Commercial paper	—	23,854	—	23,854
Total cash equivalents	$ 26,091	$ 29,028	$ —	$ 55,119
Marketable securities				
Corporate bonds	$ —	$ 96,879	$ —	$ 96,879
Commercial paper	—	122,664	—	$ 122,664
Total marketable securities	$ —	$ 219,543	$ —	$ 219,543
Total	$ 26,091	$ 248,571	$ —	$ 274,662

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

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

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

Marketable Debt Securities

The following table summarizes the Company's marketable debt securities as of March 31, 2021:

	At March 31, 2021				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
Corporate bonds	$ 102,030	$ 68	$ (45)	$ —	$ 102,053
Commercial paper	146,551	2	(35)	—	146,518
Total	$ 248,581	$ 70	$ (80)	$ —	$ 248,571

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

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

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

	At March 31, 2021	At December 31, 2020
Due in one year	$ 242,579	$ 132,056
Due after one year through three years	5,992	10,757
Total	$ 248,571	$ 142,813

4. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following:

	March 31, 2021	December 31, 2020
Prepaid external research and development expenses	$ 2,132	$ 1,421
Inventories	1,180	665
Other prepayments	4,634	4,930
VAT receivable	894	2,780
Construction deposit - current	1,634	1,552
Non-trade receivables	2,030	2,017
Total prepaid expenses and other current assets	$ 12,504	$ 13,365

5. Property and Equipment, net

Property and equipment, net consisted of the following:

	March 31, 2021	December 31, 2020
Property and equipment:		
Lab equipment	$ 5,159	$ 5,114
Leasehold improvements	2,486	2,522
Furniture and fixtures	304	304
Office and computer equipment	765	763
Construction-in-process	601	302
Property and equipment	$ 9,315	$ 9,005
Less: accumulated depreciation	(4,724)	(4,224)
Property and equipment, net	$ 4,591	$ 4,781

Depreciation expense was $0.5 million and $0.5 million for the three months ended March 31, 2021 and 2020, respectively.

6. Other Assets

Other assets consist of the following:

	March 31, 2021	December 31, 2020
Intangible assets - license milestones	$ 4,914	$ 3,076
Deferred tax assets	4,449	5,219
Deposits	1,019	1,144
Deferred financing costs	647	975
Other non-current assets	2,061	1,554
Construction deposits - long-term	6,491	6,572
Total other assets	$ 19,581	$ 18,540

7. Accrued Expenses and Other Liabilities

Accrued expenses and other liabilities consisted of the following:

	March 31, 2021	December 31, 2020
Accrued external research and development expenses	$ 8,210	$ 8,878
Accrued payroll and related expenses	7,084	11,881
Accrued professional fees	758	791
Accrued other	3,616	3,401
Accrued milestone payments	4,914	3,076
Strimvelis loss provision - current portion	1,090	916
Total accrued expenses and other liabilities	$ 25,672	$ 28,943

During the three months ended March 31, 2021, the Company accrued regulatory and commercial-related milestone payments associated with license intangibles of $1.8 million. There were no license intangibles accrued during the three months ended March 31, 2020.

8. Notes Payable

In May 2019, as amended in April 2020, the Company entered into a senior term facilities agreement (the “Credit Facility”) with MidCap Financial (Ireland) Limited (“MidCap Financial”), as agent, and additional lenders from time to time (together with MidCap Financial, the “Lenders”), to borrow up to $75.0 million in term loans. To date, the Company has borrowed $25.0 million under an initial term loan. The remaining $50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a $25.0 million term loan available no earlier than July 1, 2020 and no later than March 31, 2021 upon submission of certain regulatory filings and evidence of the Company having $100 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. 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 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 Borrower 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.

Notes payable consist of the following:

	At March 31, 2021	At December 31, 2020
Notes payable, net of issuance costs	$ 24,687	$ 24,659
Less current portion	(6,944)	(4,861)
Notes payable, net of current portion	17,743	19,798
Accretion related to final payment	465	406
Notes payable, long term	$ 18,208	$ 20,204

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

	Aggregate Minimum Payments
2021 (April - December)	4,861
2022	8,333
2023	8,334
2024	4,597
2025	—
Thereafter	—
Total	26,125
Less: current portion	(6,944)
Less: unamortized portion of final payment	(660)
Less: unamortized debt issuance costs	(313)
Notes payable, long term	$ 18,208

During the three months ended March 31, 2021 and 2020, the Company recognized $0.5 million and $0.6 million of interest expense, respectively, related to the initial term loan. The effective annual interest rate for the three months ended March 31, 2021 on the outstanding debt under the term loan was approximately 8.6%.

9. Share-Based Compensation

The Company maintains four equity compensation plans; the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"), the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "2018 Plan"), the 2018 Employee Share Purchase Plan (the "ESPP"), and the 2020 Inducement Equity Plan (the "Inducement Plan"). The board of directors has determined not to make any further awards under the 2016 plan following the Company's IPO. As of March 31, 2021, 3,542,397 shares remained available for issuance under the 2018 Plan, 1,000,000 shares remained available for issuance under the Inducement Plan, and 1,470,104 shares remained available for issuance under the ESPP.

Share option activity

The following table summarizes option activity under the plans for three months ended March 31, 2021:

	Number of Options	Weighted Average Exercise Price
Outstanding at December 31, 2020	13,895,643	$ 7.96
Granted	4,506,256	5.97
Exercised	(1,319,493)	2.06
Forfeited	(1,192,274)	11.16
Outstanding at March 31, 2021	15,890,132	$ 7.65
Vested and expected to vest, as of March 31, 2021	15,890,132	$ 7.65
Exercisable, March 31, 2021	6,116,939	$ 6.73

The weighted-average grant date fair value of share options granted during the three months ended March 31, 2021 was $3.87 per share.

Restricted Share Units

Performance-based 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.

In April 2020, the Company granted 195,000 performance-based RSUs with a total grant date fair value of $1.4 million to its Chief Executive Officer, Bobby Gaspar, M.D., Ph.D. The award vests on January 2, 2024 as to 1/3 of the award for each of the first three to occur of four milestones, if each such milestone is achieved by the Company on or before December 31, 2023 and Dr. Gaspar remains continuously employed with the Company through January 2, 2024. The milestones relate to achievement of specific clinical and regulatory milestones. No performance-based share unit performance conditions associated with this award were deemed probable and none vested during the three months ended March 31, 2021.

The maximum aggregate total fair value of the outstanding performance-based RSUs is $3.5 million. The fair value associated with the shares that could vest based on the market-based condition was 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. In the fourth quarter of 2020, the Company determined that a performance milestone was probable upon approval of Libmeldy by the European Commission in December 2020, and recognized $1.2 million in compensation cost. The shares associated with recognition of this performance milestone vested and were issued in January 2021. The Company determined that, as of March 31, 2021, none of the two remaining regulatory and research and development milestones were deemed probable.

Time-based restricted share units

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

The following table summarizes award activity for the three months ended March 31, 2021:

	Performance-based RSUs	Time-based RSUs	Total RSUs	Weighted Average Grant Date Fair Value
Unvested and outstanding at December 31, 2020	464,000	180,000	644,000	$ 8.75
Granted	—	20,000	20,000	5.98
Vested	(89,667)	—	(89,667)	9.40
Forfeited	(34,500)	(40,000)	(74,500)	11.80
Unvested and outstanding at March 31, 2021	339,833	160,000	499,833	$ 7.99

The amount of compensation cost recognized for the three months ended March 31, 2021 and 2020 for the market condition associated with the performance-based RSUs was not material.

Share-based compensation expense

Share-based compensation expense recorded as research and development and general and administrative expenses is as follows:

	March 31, 2021	March 31, 2020
Research and development	$ 2,876	$ 3,110
General and administrative	3,392	6,369
Total share-based compensation	$ 6,268	$ 9,479

During the three months ended March 31, 2020, the Company recognized $2.7 million of share-based compensation expense to selling, general and administrative expense related to the modification of share option awards associated with the separation of the Company's former Chief Executive Officer.

As of March 31, 2021, total unrecognized compensation cost related to unvested share options and time-based RSU's was approximately $53.5 million. This amount is expected to be recognized over a weighted average period of approximately 2.9 years. As of March 31, 2021, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $3.5 million, dependent upon achievement of the aforementioned milestones.

10. License Agreements

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, and option rights exercisable upon completion of clinical proof of concept studies for three additional earlier-stage development programs, which option rights have all subsequently lapsed. The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations, resulting in total consideration of $133.6 million, which was recorded in the second quarter of 2018.

The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher ("PRV") from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDT, the first of which GSK retained beneficial ownership over. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As part of the GSK Agreement the Company is also required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, 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.

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and the Company-developed product candidate, 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 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.

Telethon-OSR research and development collaboration and license agreements

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

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones, up to an aggregate of approximately €31.0 million ($36.2 million at March 31, 2021). Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses of the collaboration programs.

In May 2019, the Company entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Company an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's *ex vivo* autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I ("MPS-I"), including the Hurler variant ("MPS-IH"). Under the terms of the agreement, Telethon-OSR received €15.0 million in upfront and milestone payments from the Company upon entering into the agreement, resulting in $17.2 million in in-process research and development expense. The Company is also required to pay up to €28.0 million ($32.8 million at March 31, 2021) related to milestone payments contingent upon achievement of certain development, regulatory and commercial milestones. Additionally, the Company will be required to pay Telethon a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

Oxford BioMedica license, development and supply agreement

In November 2016, and amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica plc whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and whereby Oxford BioMedica will provide process development services ("Oxford BioMedica Development Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Development Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and fourth milestones were achieved, and the Company issued 150,826 ordinary shares. No milestones were met during the three months ended March 31, 2020. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million which was recorded to research and development expense. The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

11. Income Taxes

The Company recorded income tax expense of $1.1 million and income tax benefit of $0.3 million for the three months ended March 31, 2021 and 2020, respectively, which relates to the Company's subsidiary operations in Europe and the U.S. The income tax expense for the three months ended March 31, 2021 was primarily due to share-based compensation shortfalls. The income tax benefit for the three months ended March 31, 2020 was the result of share-based compensation windfalls.

12. Commitments and Contingencies

Legal proceedings

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

Manufacturing and technology development master agreement with AGC Biologics

The Company is party to an Agreement with AGC Biologic S.p.A ("AGC") pursuant to which the Company is obligated to pay AGC for a minimum product manufacturing commitment, dedicated manufacturing and development resources, and for a lease component associated with the right of use of exclusive manufacturing suites within AGC's existing facilities. The following table outlines the current commitments associated with the agreement, as of March 31, 2021:

Due in:	Product manufacturing commitments	Dedicated manufacturing and development resources	Exclusive transduction suites	Total remaining AGC commitment
2021 (April - December)	$ 2,379	$ 7,796	$ —	$ 10,175
2022	3,173	8,143	3,202	14,518
2023	3,173	8,143	3,202	14,518
2024	3,173	8,143	3,202	14,518
2025	1,586	4,072	1,601	7,259
Total manufacturing commitments	13,484	36,297	11,207	60,988

*Tabular disclosure above has been translated to U.S. Dollar, from Euro, using an exchange rate of €1.00 to $1.175.

Lease commitments

The Company leases office and laboratory space and has an embedded lease at AGC. There have been no material changes to the Company's lease commitments as reported in the Company's Annual Report on Form 10-K.

13. Employee Benefit Plans

The Company makes contributions to private defined contribution employee benefit plans on behalf of its employees. The Company provides employee contributions of up to six percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid $0.5 million and $0.6 million in matching contributions for the three months ended March 31, 2021 and 2020, respectively.

14. Related Party Transactions

GSK

In April 2018, the Company completed 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-OSR (see Note 10).

As of March 31, 2021, and December 31, 2020, the Company had accounts payable and accrued expenses due to GSK of nil and $0.1 million, respectively. During the three months ended March 31, 2021 and 2020 the Company made payments of $0.1 million and nil, respectively, to settle accounts payable due to GSK. During the three months ended March 31, 2021 and 2020, there were no sales of Strimvelis and the Company incurred no royalties due to GSK.

Item 2. 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 Quarterly Report on From 10-Q. Some of the information contained in this discussion and analysis and set forth elsewhere in this Quarterly Report on Form 10-Q, 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 II—Item 1A of this Quarterly Report on Form 10-Q and also in the Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Business Overview

Orchard Therapeutics is a global gene therapy company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous hematopoietic stem cell ("HSC") gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. We have one of the deepest and most advanced gene therapy pipelines in the industry spanning multiple therapeutic areas where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

Since our inception in 2015, we have devoted substantially all of our resources to conducting research and development of our product candidates, in-licensing and acquiring rights to our product candidates, business planning, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of equity securities, including American Depositary Shares ("ADSs") in our initial public offering ("IPO") and follow-on offering, ordinary shares in our private placement, and convertible preferred shares. We have also financed our operations through proceeds from our senior term facilities agreement (the "Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), research grants from the California Institute of Regenerative Medicine ("CIRM") and through proceeds associated two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program.

We have incurred significant operating losses since our inception. We will not generate revenue from product sales, except from potential future sales of Strimvelis, a commercial product we acquired in April 2018, and Libmeldy, for which we received standard marketing authorization by the European Commission in December 2020, unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. With the approval of Libmeldy in Europe, we are now focused on our transition from a primarily clinical development stage company to a commercial stage company. We plan to continue the implementation of our commercialization plan for Libmeldy and our near-term plans for commercialization include:

- Enabling patient identification via multi-pronged diagnostics initiatives and newborn screening in Europe and the U.S.;
- Expanding global footprint by qualifying leading centers with transplant and disease area expertise;
- Leveraging cross-border and treatment abroad reimbursement pathways in Europe, Middle East, and Turkey;
- Securing market access via multi-stakeholder engagement with various payment models.

Our net losses were $35.2 million and $50.6 million for the three months ended March 31, 2021 and 2020, respectively. As of March 31, 2021, we had an accumulated deficit of $640.8 million. As of March 31, 2021, we had cash, cash equivalents and marketable securities of $298.4 million, excluding amounts held in escrow deposits. Our losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, government contracts or other strategic transactions. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all.

Recent Developments

In December 2020, the European Commission granted standard marketing authorization for Libmeldy (OTL-200) (atidarsagene autotemcel) for the treatment of early onset MLD characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and

before the onset of cognitive decline). We expect to launch Libmeldy in Europe and generate product sales as early as the first half of 2021.

On February 9, 2021, we issued and sold (i) 20,900,321 ordinary shares, nominal value £0.10 per share, at a purchase price of $6.22 per share (the "Purchase Price"), which was the closing sale price of our ADSs on the Nasdaq Global Select Market on February 4, 2021, and (ii) 3,215,434 non-voting ordinary shares, nominal value £0.10 per share, at the Purchase Price (together (i) and (ii) the "Private Placement"). The Private Placement resulted in net proceeds to us of $143.7 million after deducting placement agent fees of $6.0 million and other offering-related costs of $0.3 million. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement we entered into with the purchasers named therein on February 4, 2021. The ADSs representing the ordinary shares issued in the Private Placement were registered for resale on an automatic shelf registration statement on Form S-3 filed with the SEC on April 8, 2021.

Business update regarding COVID-19

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

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

Travel and stay-at-home orders could adversely affect our contract manufacturers and third-party logistics providers. To date, our third-party contract development and manufacturing organization (CDMO) partners have continued to operate at or near normal levels. While we currently do not anticipate any interruptions, it is possible that the COVID-19 pandemic and response efforts may have an impact in the future on our or our third-party suppliers' and CDMO partners' ability to manufacture our products in development. We have reviewed the collectability and valuation of our assets through the date of financial statement issuance and did not identify any significant recoverability concerns or impairments. Any prolonged material disruptions to our employees, suppliers, CDMOs, vendors or patients could impact our operating results and could lead to impairments. To date the Company has recorded impairments on long-lived assets that are due to a combination of a corporate restructuring and COVID-19 market impacts.

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

For additional information on the various risks posed by the COVID-19 pandemic, please see the section titled "Item 1A. Risk Factors" included in this report and our Annual Report on Form 10-K filed with the SEC on March 2, 2021.

Components of our results of operations

Revenue

During the quarters ended March 31, 2021 and 2020, we recognized no revenue from sales of Strimvelis or Libmeldy. Libmeldy received approval from the EC in December 2020 and, if we are able to identify patients and secure reimbursement for our treatment, we may begin to generate revenue from the sale of Libmeldy in Europe in 2021. Strimvelis is distributed exclusively at the San Raffaele Hospital in Milan, Italy. While we expect that any future sales of Strimvelis will fluctuate quarter over quarter, we paused treating new patients with Strimvelis in October 2020 upon learning that a patient treated with the drug in 2016 under a compassionate use program was diagnosed with lymphoid T cell leukemia, a known risk factor for gammaretroviral vector-based gene therapy. The EMA's Committee for Medicinal Products for Human Use, or CHMP, reviewed the updated risk-benefit assessment of Strimvelis as part of its ongoing MAA renewal procedure, concluded that the risk-benefit balance remains favorable and recommended in February 2021 that the marketing authorization for Strimvelis be renewed for five years, and we are currently able to resume sales of Strimvelis.

Cost of product sales

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

Operating expenses

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts and the development of our product candidates, and include:

- expenses incurred under agreements with third parties, including contract research organizations (CROs) that conduct research, preclinical activities and clinical trials on our behalf as well as contract manufacturing organizations that manufacture lentiviral vectors and cell-based drug products for use in our preclinical and clinical trials;
- expenses to acquire technologies to be used in research and development;
- salaries, benefits and other related costs, including share-based compensation expense, for personnel engaged in research and development functions;
- costs 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 costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid expenses or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. Amortization of the Strimvelis loss provision is also recorded as an offset to research and development expense (See Note 2 of our condensed consolidated financial statements).

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and contract manufacturing organizations in connection with our preclinical and clinical development activities. License fees and other costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. License fees and other costs incurred prior to designating a product candidate for development are included in unallocated costs. We do not allocate employee costs, costs associated with our early-stage discovery efforts, laboratory supplies, and facilities, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials or the manufacturing requirements to conduct those clinical trials. We expect that our research and development expenses will remain consistent quarter over quarter for the near term as we continue to: (i) expedite the clinical development and continue to seek to obtain marketing approval for our lead product candidates, including OTL-200 in the U.S. for MLD and OTL-103 for WAS in the U.S. and Europe; (ii) initiate additional clinical trials for our product candidates, which may include OTL-102 for X-CGD, OTL-201 for MPS-IIIA, and OTL-203 for MPS-IH; (iii) reduce our investment in and development expenses for OTL-101 for ADA-SCID and OTL-300 for TDT and reallocate those financial resources to other programs; (iv) seek to improve the efficiency and scalability of our outsourced manufacturing processes and supply chain; (v) build process development and analytical capabilities in the near term, and potential manufacturing capabilities in the longer term; and (vi) continue to discover and develop additional product candidates. For example, in April 2020, we announced our intention to accelerate our research and development efforts for projects in less rare indications, including two new research programs in genetic subsets of frontotemporal

dementia (FTD) and Crohn's disease, and in November 2020 we announced a new program in amyotrophic lateral sclerosis (ALS). We also expect to incur additional expenses related to milestone, royalty payments and maintenance fees payable to third parties with whom we have entered into license agreements to acquire the rights related to our product candidates.

The continued commercialization of Strimvelis, the success of our efforts to build a commercial infrastructure and commence sales of Libmeldy, and the successful development and commercialization of our other 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 attractive new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates, including maintaining or resuming enrollment as a result of the COVID-19 pandemic;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- 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 post-marketing commitments for regulatory compliance for Libmeldy and Strimvelis in Europe;
- qualifying for, obtaining, and/or maintaining, adequate coverage and reimbursement by government and private payors for Libmeldy, Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Libmeldy, Strimvelis and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Strimvelis, Libmeldy, and our current and future product candidates, if approved, as viable treatment options with acceptable long-term 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 or product candidate could mean a significant change in the costs and timing associated with the development of that product or 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. If the EMA or another regulatory body determines that the safety profile of Strimvelis is no longer acceptable as a result of the adverse event described above, our ability to commercialize Strimvelis would be impaired.

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.

While general and administrative expenses declined approximately 30% in the first quarter of 2021 as compared to the first quarter of 2020 due to our corporate restructuring, we expect that our general and administrative expenses will remain steady in the near term. We note that our selling costs are likely to increase as we continue to expand our organization into multiple countries in Europe to support the planned launch of Libmeldy, which received marketing authorization in the EU in December 2020 but that such increases will be offset by savings as a result of our restructuring and other initiatives.

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.

Other income (expense)

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

Results of operations

Comparison of the three months ended March 31, 2021 and 2020

The following table summarizes our results of operations for the three months ended March 31, 2021 and 2020:

	Three Months Ended March 31,		
	2021	2020	Change
	(in thousands)		
Product sales, net	$ —	$ —	$ —
Costs and operating expenses			
Research and development	21,035	24,836	(3,801)
Selling, general and administrative	14,051	20,145	(6,094)
Total costs and operating expenses	35,086	44,981	(9,895)
Loss from operations	(35,086)	(44,981)	9,895
Other income (expense):			
Interest income	171	1,480	(1,309)
Interest expense	(538)	(613)	75
Other income (expense):	1,358	(6,790)	8,148
Total other income (expense), net	991	(5,923)	6,914
Loss before provision for income taxes	(34,095)	(50,904)	16,809
Income tax (expense) benefit	(1,087)	335	(1,422)
Net loss	$ (35,182)	$ (50,569)	$ 15,387

Research and development expenses

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

	Three months ended March 31		
	2021	2020	Change
	(in thousands)		
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 5,741	$ 4,732	$ 1,009
Primary immune deficiencies	2,603	4,369	(1,766)
Blood disorders	127	182	(55)
Other research and preclinical programs under development	1,030	569	461
Total direct research and development expenses:	9,501	9,852	(351)
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	8,953	10,107	(1,154)
Share-based compensation	2,876	3,110	(234)
Accretion of Strimvelis loss provision	(446)	(1,691)	1,245
Research and development tax credit	(3,554)	(3,417)	(137)
Facility and other	3,705	6,875	(3,170)
Total indirect research and development expenses	11,534	14,984	(3,450)
Total research and development expenses	$ 21,035	$ 24,836	$ (3,801)

Direct research and development expenses for neurometabolic programs increased by $1.0 million. Direct expenses associated with OTL-200 declined by $0.4 million compared to the first quarter of 2020. This was primarily due to a decline of $1.0 million in clinical development related costs, offset by an increase of $0.6 million in manufacturing costs. Direct expenses for OTL-203 increased by $0.8 million, which is primarily due to an increase of $0.6 million related to technical development costs, as well as $0.2 million in other clinical and consulting costs attributable to the program. Direct expenses for OTL-201 increased by $0.5 million compared to the first quarter of 2020, which was primarily attributable to increases in manufacturing costs of $1.1 million, offset by a decline in clinical costs of $0.6 million. Direct expenses for OTL-202 increased slightly by $0.1 million as compared to the first quarter of 2020.

Direct research and development expenses for primary immune deficiency-related programs declined by $1.8 million. Direct expenses associated with OTL-101 declined by $2.5 million, which was primarily due to the de-prioritization of this program in the second quarter of 2020 and the savings associated with the de-prioritization. These savings include a $1.7 million decline in manufacturing costs and a $0.6 million decline in clinical trial costs. Direct expenses for OTL-103 increased by $1.1 million, primarily due to a $1.5 million increase in clinical and consulting costs, offset by a $0.4 million decline in manufacturing costs. Direct expenses associated with our OTL-102 program declined by $0.4 million. Direct expenses for Strimvelis were flat as compared to the first quarter of 2020.

Direct research and development expenses for blood disorder-related programs declined by $0.1 million in the first quarter of 2021. We expect that OTL-300 costs will continue to be minimal as we have reduced our investment and development in the program. The increase in costs of $0.5 million associated with other research and preclinical programs primarily relates to increased spend on programs such as OTL-204 for FTD, OTL-104 for Crohn's, and other undisclosed pre-clinical programs. We expect these costs to continue to increase as part of our plan to focus on HSC gene therapy for larger indications.

Unallocated research and development costs and offsets to research and development expenses declined by $3.5 million. This is primarily due to a decline in personnel related costs of $1.2 million as a result of our strategic restructuring, which occurred in the second quarter of 2020. Other facility, travel, and unallocated platform-related research and development costs have declined by $3.2 million. This was driven by a $0.5 million decline in travel costs due to travel restrictions in response to the COVID-19 pandemic, a decline of $2.1 million in unallocated platform-related manufacturing costs, and a decline of $0.4 million in facilities costs as we have subleased our former Fremont manufacturing facility at the end of 2020 and no longer incur significant costs associated with the facility. Our UK research and development tax credit, which is recorded as an offset to research and development expense, increased by $0.1 million. Accretion of the Strimvelis loss provision, which is also accounted for as an offset to research and development expense, declined by $1.2 million as we have adjusted our ongoing estimate due to our reduction of investment in OTL-101 and have extended out the expected period of losses for Strimvelis, which results in lower amortization of the loss provision in a given period.

Selling, general and administrative expenses

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

	Three months ended March 31,		
	2021	2020	Change
	(in thousands)		
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 5,493	$ 6,759	$ (1,266)
Share-based compensation	3,392	6,383	(2,991)
Consulting, professional, and insurance-related costs	2,954	2,878	76
Marketing, promotions, and advocacy	1,103	2,148	(1,045)
Facilities and other costs	1,109	1,977	(868)
Total selling, general, and administrative expenses:	$ 14,051	$ 20,145	$ (6,094)

Selling, general and administrative expenses were $14.1 million in the first quarter of 2021, compared to $20.1 million in the first quarter of 2020. The decline of $6.1 million was primarily due to a $0.7 million severance charge and $2.7 million share-based compensation charge associated with the separation of our former Chief Executive Officer in March 2020, that did not recur in the first quarter of 2021. Further, personnel costs declined as we realized savings associated with our corporate restructuring that took place in 2020. Consulting, professional, and insurance costs stayed relatively flat, with slight declines in professional and legal costs of $0.2 million offset by an increase in insurance expense of $0.2 million. Expenses associated with marketing and commercialization of Strimvelis, and costs associated with increased promotional and advocacy activities in preparation for the potential future commercialization of our product candidates, if approved, declined by $1.0 million due to lower marketing costs for Strimvelis as well as our corporate strategy pivot. Market access fees, a component of marketing, promotions, and advocacy costs, remained flat. Facilities and other costs declined by $0.9 million, primarily due to a $0.4 million decline in travel expenses, as well as general reductions in facilities and IT-related costs associated with our corporate restructuring.

Other income (expense), net

Other income (expense), net for the first quarter of 2021 and 2020 consisted of income of $1.0 million and expenses of $5.9 million, respectively. During the first quarter of 2021, we had net realized and unrealized gains on foreign currency transactions of $1.4 million, compared to net realized and unrealized losses of $6.8 million for the first quarter of 2020. These unrealized losses are driven primarily by intercompany balances denominated in currencies other than our functional currency, the U.S. Dollar, and typically fluctuates concurrently with fluctuations in the U.S. Dollar to Pounds sterling exchange rate. Additionally, we had interest income of $0.2 million in the first quarter of 2021, compared to $1.4 million in the first quarter of 2020. The decline is primarily due to a lower investment portfolio balance as of March 31, 2021 as compared to March 31, 2020. The decline in interest expense of $0.1 million in the first quarter of 2021 as compared to the first quarter of 2020 is attributable to lower interest rates on our Credit Facility, which is pegged to LIBOR.

Liquidity and capital resources

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

On February 27, 2020 we entered into a Sales Agreement with Cowen and Company, LLC, as agent, relating to an “at the market offering,” pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. As of March 31, 2021, we have not sold any shares under the Sales Agreement.

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

Cash flows

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

	Three months ended March 31,	
	2021	2020
	(in thousands)	
Net cash used in operating activities	$ (39,242)	$ (49,902)
Net cash (used in) provided by investing activities	(83,526)	56,814
Net cash provided by financing activities	146,434	1,438
Effect of exchange rate changes on cash and cash equivalents	82	(303)
Net increase in cash, cash equivalents, and restricted cash	$ 23,748	$ 8,047

Operating activities

During the first quarter of 2021, operating activities used $39.2 million of cash, primarily resulting from our net loss of $35.2 million. Cash usage from changes in our operating assets and liabilities was $13.3 million, which was primarily driven by an increase in our research and development tax credit receivable of $3.6 million and a decline in accounts payable and accrued expenses of $8.9 million. The decline in accounts payable and accrued expenses is primarily attributable to the cash payout of the 2020 annual bonuses of $7.2 million in the first quarter of 2021. Non-cash adjustments to operating activities of $9.2 million was generally due to $6.3 million in non-cash share-based compensation expense, offset by $0.4 million in amortization of the Strimvelis loss provision as an offset to research and development expense. Further, there were unrealized foreign currency transaction losses on investments and intercompany accounts by our UK subsidiary of $1.4 million, which are an add-back to cash flows from operating activities.

During the first quarter of 2020, operating activities used $49.9 million of cash, primarily resulting from our net loss of $50.6 million. Cash usage from changes in our operating assets and liabilities was $14.1 million, which was primarily driven by an increase in our research and development tax credit receivable of $3.4 million and a decline in accounts payable and accrued expenses of $8.0 million. The decline in accounts payable and accrued expenses is primarily attributable to the payout of our annual bonuses of $9.0 million in the first quarter of 2020. Non-cash adjustments to operating activities of $14.8 million was generally due to $9.5 million in non-cash share-based compensation expense, offset by $1.7 million in amortization of the Strimvelis loss provision as an offset to research and development expense. Further, there were unrealized foreign currency transaction losses on investments and intercompany accounts by our UK subsidiary of $6.4 million that were driven by the strengthening of the U.S. dollar.

Investing activities

During the first quarter of 2021 and 2020, we used $83.5 million and generated $56.8 million, respectively, of cash in investing activities. The increase in cash used for investing activities in the first quarter of 2021 compared to the first quarter of 2020 is attributable to purchases of marketable debt securities of $130.4 million in the first quarter of 2021, as compared to nil purchases in the first quarter of 2020. Proceeds from the sales and maturities of marketable securities were $47.2 million in the first quarter of 2021, as compared to $68.1 million in the first quarter of 2020. Further in the first quarter of 2020, we made a $10 million construction deposit associated with our former Fremont, California manufacturing facility, which did not recur in the first quarter of 2021.

Financing activities

During the first quarter of 2021, we had net proceeds from the issuance of ordinary shares in our private placement of $143.9 million after payment of $6.1 million in offering costs. During the first quarter of 2020, we did not have any proceeds from the issuance of ordinary shares in any private or public offerings.

Funding requirements

We expect our expenses and capital expenditures will remain consistent in the near term in connection with our ongoing activities as we advance the preclinical activities and clinical trials of our product candidates and as we:

- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of Strimvelis in the European Union and planned commercial launch of Libmeldy in Europe, 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;
- perform research and development activities with respect to potential new product candidates;
- conduct investigational new drug application, or IND, and or clinical trial application, or CTA,-enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates;
- seek to identify and develop, acquire or in-license additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates, to support technology and process innovations and to support manufacturing of product to commercial scale;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe our existing cash, will enable us to fund our operating expenses and capital expenditure requirements into the first half of 2023. 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 condensed consolidated financial statements are prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of our financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that of our critical accounting policies which are described under the heading “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Significant Judgments and Estimates” in our Annual Report, the following accounting policies involve the most judgment and complexity:

- United Kingdom research and development tax credit
- Accrued research and development expenses
- Valuation of share-based compensation

Accordingly, we believe the policies set forth above are critical to fully understanding and evaluating our financial condition and results of operations. If actual results or events differ materially from the estimates, judgments and assumptions used by us in applying these policies, our reported financial condition and results of operations could be materially affected. There have been no material changes to our critical accounting policies since December 31, 2020.

Off-balance sheet arrangements.

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate sensitivity

As of March 31, 2021, we had cash, cash equivalents, marketable securities, and restricted cash of $298.4 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying UK and US bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We have borrowed $25.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 6% plus LIBOR. As of March 31, 2021, the carrying value of the term loans under the credit facility was $25.2 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. Exchange gains or losses arising from foreign currency transactions are included in the determination of net loss for the respective periods. We recorded net realized and unrealized foreign currency gains of $1.4 million and losses of $6.6 million for the three months ended March 31, 2021, and 2020, respectively. These foreign currency transaction gains and losses are primarily related to revaluation of intercompany balances denominated in currencies other than the U.S. dollar. The losses are included in other income (expense), net in our condensed consolidated statements of operations and comprehensive loss.

Assets and liabilities have been translated at the exchange rates at the balance sheet dates, while revenue and expenses are translated at the average exchange rates over the reporting period and shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net loss but are included in our foreign 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 4. Controls and Procedures.

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) or 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act) that are designed to ensure that information required to be disclosed in reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this report. In designing and evaluating our disclosure controls and procedures, our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial officer have concluded based upon the evaluation described above that, as of March 31, 2021, our disclosure controls and procedures were effective at the reasonable assurance level.

We continue to review and document our disclosure controls and procedures, including our internal controls and procedures for financial reporting, and may from time to time make changes aimed at enhancing their effectiveness and to ensure that our systems evolve with our business in accordance with the Exchange Act.

Changes in Internal Control Over Financial Reporting

During the three months ended March 31, 2021, there have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) or 15d-15(d) under the Exchange Act) that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II—OTHER INFORMATION

Item 1. 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 March 31, 2021, we were not a party to any material legal proceedings.

Item 1A. Risk Factors.

Item 1A. Risk Factors.

Our business faces significant risks. This section of the Quarterly 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 Quarterly 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 prospects. This Quarterly 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 Quarterly 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 $35.2 million and $50.6 million for the three months ended March 31, 2021 and 2020, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares and through sales of our ADSs in our initial public offering and follow-on offering. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union, building a global commercial infrastructure to support commercialization of our product candidates, including Libmeldy (OTL-200) and OTL-103 for Wiskott Aldrich syndrome, or WAS, if such product candidates are approved, as well as expanding our team. Prior to the approval of Libmeldy in Europe in December 2020, Strimvelis was our only product that had been approved for sale. Absent the realization of sufficient revenues from product sales of Libmeldy and Strimvelis, and from sales of our current or future product candidates, if approved, we may never attain profitability.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially over time if, and as, we:

- seek marketing approvals for our product candidates that successfully complete clinical trials or meet primary endpoints, if any;
- complete our build-out of our commercial operations in preparation to launch, market and sell Libmeldy in Europe and grow such infrastructure for the commercialization (or anticipated commercialization) of any product candidates for which we may submit for and obtain marketing approval anywhere in the world;
- continue to support a sales, marketing and distribution infrastructure for Strimvelis in the European Union;
- continue our development of our product candidates, including continuing our ongoing advanced registrational trials and supporting studies of OTL-200 for MLD and OTL-103 for WAS, our ongoing and planned clinical trials of OTL-102 for X-linked chronic granulomatous disease, or X-CGD, OTL-203 for mucopolysaccharidosis type I Hurler variant, or MPS-IH, and OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- continue our ongoing clinical trials and any required regulatory updates for OTL-101 for adenosine deaminase severe combined immunodeficiency, or ADA-SCID, and OTL-300 for transfusion-dependent beta-thalassemia, or TDT;
- conduct investigational new drug application, or IND, or clinical trial application, or CTA, enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates or future product candidates, including new research programs in genetic subsets of frontotemporal dementia, or FTD, and Crohn's disease;
- seek to identify and develop, acquire or in-license additional product candidates or technologies;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates, to support technology and process innovation, and to support manufacturing of product to commercial scale;

- establish partnerships with contract development and manufacturing organizations, or CDMOs;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility in the long-term;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality, regulatory affairs, process development and control, manufacturing, supply chain, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- encounter delays or setbacks in the preclinical testing, enrollment or conduct of our clinical trials for our product candidates, encounter delays in regulatory review timelines, such as for our marketing authorization application, or MAA, under review by the European Medicines Agency, or EMA, or experience high levels of absenteeism, due to the COVID-19 pandemic;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

In December 2020, we received standard marketing authorization for Libmeldy in the European Union as well as the United Kingdom, Iceland, Liechtenstein and Norway. Although we are preparing to launch the commercialization of Libmeldy in Europe, to date Strimvelis is our only product that we have sold and, to date, it has only been approved for sale 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. There is no assurance that sales of Strimvelis will resume, and even if resumed, 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, 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 Libmeldy or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

We have only generated revenue from sales of Strimvelis to date, and we may never be profitable.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully develop and commercialize products. Although we have generated revenue from the sale of Strimvelis, we do not expect to achieve profitability unless and until we successfully commercialize Libmeldy in Europe and complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. For example, in connection with the GSK Agreement, 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 attractive new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates, including maintaining or reaching target enrollment levels and collecting the necessary follow-up data during the COVID-19 pandemic;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing Libmeldy in Europe and other product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related post-marketing commitments for regulatory compliance for Libmeldy and Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Libmeldy and Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and

the market demand for Libmeldy and Strimvelis, if sales are resumed, and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Libmeldy and Strimvelis, if sales are resumed, 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 Libmeldy in Europe and any other products for which we obtain marketing approval. Our expenses could increase beyond expectations if we are required by the United States Food and Drug Administration, or the FDA, or the EMA or other regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate or if we encounter delays or clinical holds in the development of our product candidates. Even if we commercialize Libmeldy in Europe, resume generating 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 during the first quarter of 2021, primarily due to our net loss of $35.2 million for that period. We expect our expenses to increase in connection with our ongoing activities, particularly as we prepare to launch the commercialization of Libmeldy in Europe, continue to support our commercial infrastructure in support of Strimvelis, if sales resume, and our anticipated commercialization of OTL-103 for WAS, if 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. In addition, we expect to incur significant expenses related to product sales, post-marketing regulatory commitments, medical affairs, marketing, manufacturing, distribution and quality systems to support Libmeldy and Strimvelis, if sales resume, 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. 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 success of our commercialization efforts and market acceptance of Libmeldy in Europe;
- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities required, including quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution, to support Libmeldy in Europe, Strimvelis in the European Union, if sales resume, 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 Libmeldy and Strimvelis, if sales resume, and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related post-marketing commitments for regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our product candidates or future product candidates, including the need to conduct long-term follow-up for up to 15 years for our development programs and additional clinical trials to support marketing approvals for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs, including our ability to resolve delays in trial enrollment as a result of the COVID-19 pandemic;

- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Libmeldy and Strimvelis, if such sales resume, and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

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

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

We may seek to raise capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise capital through the sale of equity, convertible debt securities or other equity-based derivative securities, ownership percentages of all our shareholders may be diluted and the terms may include liquidation or other preferences that adversely affect their rights as shareholders. Any additional indebtedness we incur would result in additional increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our ADSs to decline and existing shareholders may not agree with our financing plans or the terms of such financings. If we raise funds through strategic partnerships 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. The significant volatility in public equity markets and the disruptions to the U.S. and global economies caused by the COVID-19 pandemic may make it more difficult to raise capital through sales of our ADSs on favorable terms, or at all.

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

We were incorporated in August 2018 to become a holding company for Orchard Therapeutics (Europe) Limited, which was founded in 2015, and its subsidiaries. Our operations, to date, have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring certain of our product candidate portfolios and rights to our technology, identifying potential product candidates, undertaking preclinical studies and planning and supporting clinical trials of our product candidates, establishing research and development and manufacturing capabilities, establishing a quality management system, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union, if sales resume, and building a global commercial infrastructure to support commercialization of Libmeldy and OTL-103 for WAS, if approved. We have not yet demonstrated the ability to manufacture products on a commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they 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 Libmeldy and OTL-103 for WAS, if approved, we may experience delays in establishing a sustainable, reproducible and scalable manufacturing capability with commercial CDMO partners, which may prevent us from commercializing our product candidates for which we obtain marketing approval on a timely or profitable basis, if at all.

In addition, the clinical trial requirements of the FDA, EMA and other foreign regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate can vary substantially, for example, based upon the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. To date, only a limited number of gene therapies have received marketing authorization from the FDA or EMA. We have limited experience in preparing, submitting and maintaining regulatory submissions. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States, Europe or in other jurisdictions, or how long it will take to commercialize Libmeldy in Europe or any other product candidates for which we obtain marketing approval. Approvals by the EMA may not be indicative of what the FDA may require for approval, and vice versa.

The results from our clinical trials for OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. 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 may not be sufficiently robust to support the approval of or submission of marketing approval for our product candidates by the FDA for OTL-200 and by the FDA and EMA for OTL-103 for WAS. The FDA and/or EMA normally require two registrational trials to approve a drug or biologic product, and thus the FDA and/or EMA may require that we conduct additional clinical trials of our product candidates prior to a BLA or MAA submission. The FDA and/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.

Due to the nature of the indications our product candidates are designed to treat, and the limited number of patients with these conditions, a placebo-controlled and blinded study is not always practicable for ethical and other reasons. Accordingly, in some cases our registrational programs rely on natural history models to demonstrate clinical efficacy. While the FDA recognizes the potential for natural history models to alleviate the need for placebo arms in trials for drugs that target very rare diseases, where trial recruitment can be especially challenging, the FDA has found the use of natural history data as a historical comparator to be unsuitable for adequate and well-controlled trials in many circumstances. The FDA generally finds trials using historical controls to be credible only when the observed effect is large in comparison to variability in disease course. It is possible the FDA will not consider our comparisons to natural history data and, where available, historical transplant data or intra-subject comparison between before gene therapy and after gene therapy, to provide clinically meaningful results. Additionally, even though OTL-200 and OTL-103 for WAS have achieved the primary endpoints in their respective ongoing registrational clinical trials, the FDA has not (and in the case of OTL-103, the EMA has also not) yet approved the clinical meaningfulness of the trial results and their sufficiency to support a marketing authorization.

For example, the FDA has provided written feedback on the sufficiency of our data package for OTL-200, including the clinical endpoints, natural history analysis and chemistry and manufacturing and controls, or CMC, data package. Although the FDA cleared our IND application for OTL-200 in 2020 and we received Regenerative Medicine Advanced Therapy, or RMAT, designation in 2021, there can be no guarantee we will be successful in resolving open matters to the FDA's satisfaction before the intended BLA submission, in which case the adequacy of our clinical endpoints, natural history analysis and CMC data package to support a potential BLA submission and approval will be review issues. We have also received written feedback from the FDA on the sufficiency and adequacy of our data package for OTL-103 for WAS. The FDA has advised us that the sufficiency of such package to support a BLA submission will be a review issue and recommended that we collect additional CMC and clinical data to support any such submission. We continue to engage with the FDA as we seek to address their recommendations and identify expeditious paths to market for our product candidates.

It is possible that the FDA or EMA may recommend or require us to conduct further studies, analyses or registrational trials with respect to our product candidates, possibly involving a larger sample size or a different clinical trial design. The FDA or EMA may also require that we conduct a longer follow-up period of patients treated with our product candidates prior to accepting a BLA or MAA submission, as applicable.

In addition, data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other foreign regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. The FDA may further refer any future BLA submission to an advisory committee for review, evaluation, and recommendation as to whether the application should be approved. This review may add to the time for approval, and although the FDA is not bound by the recommendation of an advisory committee, objections or concerns expressed by the advisory committee may cause the FDA to delay or deny approval. We also may experience regulatory delays or rejections as a result of many factors, including serious adverse events, or SAEs, involving our product candidates, changes in regulatory policy or changes in requirements during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

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

It is possible that the FDA or the EMA may not consider the results of our clinical trials, including reliance on foreign clinical data, to be sufficient for approval of our product candidates. If the FDA or 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.

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 released a series of final guidance documents and a draft guidance document for consultation, which amongst other topics, included various aspects of gene therapy product development, review, and approval, including aspects relating

to clinical and manufacturing issues related to gene therapy products. We cannot be certain whether future guidance will be issued and be relevant to, or have an impact on, our gene therapy programs or the duration or expense of any applicable regulatory development and review processes.

Libmeldy, Strimvelis and our product candidates and the process for administering Libmeldy, Strimvelis and our product candidates may cause serious or undesirable side effects or adverse events or have other properties that could delay or prevent regulatory approval, limit commercial potential or result in significant negative consequences for our company.

Following treatment with our gene therapies, patients may experience changes in their health, including illnesses, injuries, discomforts or a fatal outcome. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of our product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in previous clinical trials, as well as conditions that did not occur or went undetected in previous clinical trials, will be reported by patients. Gene therapies are also subject to the potential risk that occurrence of adverse events will be delayed following administration of the gene therapy due to persistent biological activity of the genetic material or other components of the vectors used to carry the genetic material. Many times, additional safety risks, contraindications, drug interactions, adverse events and side effects are only detectable after investigational products are tested in larger scale, registrational trials or, in some cases, after they are made available to patients on a commercial scale after approval. The FDA generally requires long-term follow-up of study subjects. Although the risk profile of a gene therapy candidate is a factor in determining the adequacy of such long-term follow-up, the FDA currently recommends that sponsors observe study subjects for potential gene therapy-related adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects. If additional experience indicates that any of our product candidates or similar products developed by other companies 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.

Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. Possible adverse side effects and adverse events that may occur with treatment with gene therapy products include an immunologic reaction early after administration that could substantially limit the effectiveness of the treatment or represent safety risks for patients. Another traditional safety concern for gene therapies using viral vectors has been the possibility of insertional mutagenesis (or oncogenesis) by the vectors, leading to malignant transformation of transduced cells. There have been several adverse events and SAEs attributed to gene therapy treatments in the past, including reported cases of leukemia with the use of gammaretrovirus vector and death seen in other clinical trials. In October 2020, we were notified that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with lymphoid T cell leukemia. Subsequent findings confirmed that the patient's leukemia was due to insertional oncogenesis attributable to treatment with Strimvelis. The EMA's Committee for Medicinal Products for Human Use, or CHMP, concluded that the risk-benefit balance remains favorable and requested that the Strimvelis product information identify insertional mutagenesis (or oncogenesis) as an "important identified risk" instead of an "important potential risk" in light of this event.

Strimvelis is the only gammaretroviral vector-based gene therapy in our portfolio. Libmeldy and all of our pipeline therapies employ the self-inactivating (SIN) lentiviral vector-based approach which has been specifically designed to avoid insertional oncogenesis after administration. Although to our knowledge and as of the date of this report no evidence of insertional oncogenesis has been observed with lentiviral vector-based HSC gene therapy in any of our programs, there can be no assurance that this will continue to be the case. Moreover, while our gene therapy approach is designed to avoid immunogenicity after administration, there can be no assurance that patients would not develop antibodies that may impair treatment. Our approach involves the use of integrating vectors which have the potential for genomic disruption and therefore could interfere with other genes with adverse clinical effects. If any of our gene therapy product candidates demonstrates adverse side effects or adverse events at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

In addition to side effects and adverse events caused by our product candidates, the conditioning, administration process or related procedures also can cause adverse side effects and adverse events. A gene therapy patient is generally administered cytotoxic drugs to remove stem cells from the bone marrow to create sufficient space in the bone marrow for the modified stem cells to engraft and produce new cells. This procedure compromises the patient's immune system. While certain of our product candidates are designed to utilize milder conditioning regimens that are intended to require only limited removal of a patient's bone marrow cells, the conditioning regimens may not be successful or may nevertheless result in adverse side effects and adverse events. If in the future we are unable to demonstrate that such adverse events were caused by the conditioning regimens used, or administration process or related procedure, the FDA, the European Commission, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all target indications. Even if we are able to demonstrate that adverse events are not related to the drug product or the administration of such drug product, such occurrences could affect patient recruitment, the ability of enrolled patients to complete the clinical trial, or the commercial viability of any product candidates that obtain regulatory approval.

Additionally, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval to ensure that the benefits of our product candidates outweigh their risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, and restrictions on how or where the product can be distributed, dispensed or used. Other non-U.S. regulatory authorities could impose other specific obligations, such as through a risk management plan, or RMP, submitted to the EMA. Furthermore, if we or others later identify undesirable side effects caused by Strimvelis, Libmeldy or our product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product or product candidate;
- regulatory authorities may require additional warnings or limitations of use in product labeling;
- we may be required to change the way a product candidate is distributed, dispensed, or administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of Libmeldy and Strimvelis, if sales resume following investigation of the adverse event described above, and any other products for which we obtain marketing approval and could significantly harm our business, prospects, financial condition and results of operations.

To date, most of the clinical trials for our product candidates were conducted as investigator-sponsored clinical trials using drug product manufactured at academic sites. Regulatory authorities may closely scrutinize the data collected from these trials and may require that we conduct additional clinical trials prior to any marketing approval.

We have limited experience conducting company-sponsored clinical trials and to date most of our product candidates have been evaluated under investigator-sponsored clinical trials using drug product manufactured at the applicable or relevant academic site. We did not control the design or administration of these investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these clinical trials. Investigator-sponsored clinical trials are often conducted under less rigorous clinical and manufacturing standards than those used in company-sponsored clinical trials. For example, the drug product used in our company-sponsored clinical trials is manufactured by third party CDMOs using current good manufacturing practices, or cGMP, standards. Accordingly, regulatory authorities may closely scrutinize the data collected from these investigator-sponsored clinical trials and may require us to obtain and submit additional clinical data prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates. We will be required to demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CDMOs, and we cannot provide assurances that we will satisfy such comparability requirements. We may also be required to demonstrate improved quality and drug product manufacturing state of control in accordance with cGMP standards. For example, in the compassionate use program conducted by Great Osmond Street Hospital, or GOSH, one patient experienced an SAE, staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. A similar SAE, bacteremia, was observed in the clinical trial conducted at University of California Los Angeles, or UCLA, for OTL-101 for ADA-SCID with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. The bacteremia resolved on Day 3 without sequelae. We believe that our commercial manufacturing processes for our product candidates, together with cryopreserved formulation, which allows for safety/microbiological testing to be completed prior to drug infusion to the patient, could mitigate the risk of contamination of products that might have resulted in such infections, but there can be no assurance that this will be the case. To the extent that the results of our current company-sponsored trials are inconsistent with, or different from, the results of any investigator-sponsored trials or raise concerns regarding our product candidates, the regulatory authorities may question the results from some or all of these trials, and may require us to obtain and submit additional clinical data from drug product manufactured by CDMOs prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates.

We may be unable to demonstrate comparability between 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 (e.g., OTL-101 for the treatment of ADA-SCID), we will need to demonstrate comparability between vector and drug product manufactured by our CDMOs with vector and/or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another. In other cases, we may elect to initially seek approval of our product candidate using one cellular source only and subsequently seek approval for the use of the other cellular source. We cannot be assured that the FDA, EMA or other regulatory authority will not require us to conduct additional analytical 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 or our product candidates using these production methods and processes. For example, in connection with our OTL-200 (Libmeldy) program, the FDA has noted that we may have challenges demonstrating comparability between data collected at one manufacturing facility using bone marrow and data collected at another manufacturing facility using bone marrow or peripheral blood, and both the FDA and the EMA have advised us that they 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.

If any of the FDA, EMA or other regulatory authority does not accept our comparability data or if an adequate potency assay for a product candidate is not available or supported by such regulatory authority, our regulatory approval for such product candidate, if any, will be limited or delayed. For example, if one or more of these regulatory authorities does not accept that our cryopreservation process produces a product candidate that is comparable to our fresh drug product, our regulatory approval, if any, would be limited to our fresh product candidate until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials or require additional test method development. Potency assays that measure strength (e.g., enzymatic activity, or other relevant function) of each active ingredient are required for release testing of licensed biological drug products, comparability and stability analysis.

In certain conditions, such as MLD and ADA-SCID, the potency of a product candidate may be directly measured through enzymatic activity; however, for an intracellular protein such as WAS, developing an assay is more complex. We are therefore working with the FDA and EMA to develop appropriate approaches to assess the drug product potency of OTL-103 for the treatment of WAS, but COVID-19-related restrictions to laboratory access at our facilities and those of our third-party service providers have delayed and may continue to delay the timeline for such development. If an adequate potency assay for a product candidate, such as OTL-103, is not available, if COVID-19-related restrictions to laboratory access persist, or if the FDA, EMA or other regulatory authority require additional tests or recommend a different approach to support the potency of any of our product candidates, regulatory approval for any such product candidates will be delayed, and such regulators might request additional clinical data to support comparability analysis. Similarly, if one or more of these regulatory authorities does not accept that our drug product manufactured with HSCs derived from the patient's mobilized peripheral blood is comparable to drug product manufactured with HSCs derived from the patient's bone marrow, any regulatory approval would be limited to drug product manufactured with HSCs derived from the patient's bone marrow until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials. In April 2020, the FDA advised us that we may need to generate additional data to demonstrate the comparability of our OTL-200 drug product derived from the patient's mobilized peripheral blood and the OTL-200 drug product derived from the patient's bone marrow, and that the data provided to date are inadequate to determine if the two materials are comparable. Further, the FDA requested that we provide data that demonstrates the comparability of the different OTL-200 product formulations used across our trials. Failure to demonstrate such comparability, or if we are required to conduct additional testing or additional clinical trials, potentially at additional sites, would delay any marketing authorization and adversely affect the commercial viability of our product candidates and may adversely affect our ability to generate revenue, as a result of which our business, prospects, financial condition and results of operations may suffer.

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

As part of our strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates. We may spend several years completing our development of any particular current or future product candidates, and failure can occur at any stage. Even if we receive approval of a product candidate, we may not achieve commercial success for a variety of factors, including failure to achieve market acceptance in the medical community and the availability of third-party insurance coverage or reimbursement. For example, we received standard marketing authorization for Libmeldy in December 2020 from the European Commission and are preparing to launch the commercialization of Libmeldy in Europe in the first half of 2021, but

there is no assurance that our commercialization efforts will be successful or that our pricing assumptions or our assumptions about the size of the anticipated patient population will prove to be accurate. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. For example, in May 2020, we announced our decision to reduce investment in the development of OTL-101 for ADA-SCID and OTL-300 for TDT and to focus on other product candidates in our pipeline and new research and development efforts in less rare diseases. Our focus on the advancement of our other product candidates may ultimately prove to be unsuccessful or less successful than if we had continued to prioritize OTL-101 or OTL-300, and if we choose to reprioritize OTL-101 or OTL-300 in the future, we may experience delays that would not have otherwise occurred, due to inefficiencies from loss of organizational knowledge and ramp up costs. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

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

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as bone marrow transplantation or enzyme replacement therapy. We may never succeed in demonstrating efficacy and safety of our product candidates or any future product candidates in clinical trials or in obtaining marketing approval thereafter. Accordingly, our focus on treating rare diseases may not always result in the discovery and development of commercially viable products.

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

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

From time to time, we may publish interim data and/or ad hoc analyses from investigator-sponsored or company-sponsored clinical trials of our product candidates. Preliminary data and ad hoc analyses from these clinical trials may change as longer-term patient data become available. In general, we seek to conduct interim analyses at times we pre-specify with the applicable regulators prior to commencement of the trial, at which time we lock and reconcile the database. We may 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 Libmeldy (OTL-200) 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 provide adequate support for marketing approvals by the FDA in the case of Libmeldy and by the FDA or EMA in the case of OTL-103 without conducting further clinical trials. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical trials, and may not be repeated or observed in ongoing or future trials involving our product candidates. There is limited data concerning long-term safety and efficacy following treatment with our product candidates. For example, OTL-202 for mucopolysaccharidosis type III-B, or MPS-IIIB, has 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. Additionally, the recent COVID-19 global pandemic has had and may continue to have a sustained impact on our ability to recruit and follow-up with patients either due to continued or renewed restrictions on travel or shelter-in-place orders or policies, or due to changes in patient willingness to participate in trials or travel to study sites in the wake of the pandemic. Additionally, COVID-19 related study site policies may create delays or setbacks in our ability to continue to enroll or to dose patients. For example, the enrollment timeline for OTL-201 was initially delayed by three months, and we may face delays in the future due to the impacts of the COVID-19 pandemic. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

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

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- safety profile, to date, of the product candidate under study;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases, including any required pretreatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- degree of progression of the subject's disease at the time of enrollment;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective subjects;
- the impact of the COVID-19 global pandemic or future pandemics or similar events on patients' willingness and ability to participate in clinical trials or on study site policies;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor subjects adequately during and after treatment.

Our current product candidates are being developed to treat rare conditions. We plan to seek initial marketing approvals in the United States and the European Union. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA or EMA. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with academic partners or contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- the absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

We may encounter substantial delays in our clinical trials, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. As a result of the COVID-19 global pandemic, certain of our clinical sites have partially shifted and may continue to shift significant resources to patients with COVID-19, which extended the enrollment timeline of our OTL-201 clinical trial by three months and provided challenges for patient follow-up visits for all programs. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable patients and in sufficient volume to participate in our clinical trials;

- imposition of a clinical hold by regulatory agencies;
- failure by our academic partners, CROs, other third parties or us to adhere to clinical trial protocol and recordkeeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- delays in patient enrollment, missed assessments resulting from remote follow-up visits, or delays in completion of participation as a result of the impact of the COVID-19 global pandemic or future pandemics or similar events;
- the occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

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

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

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

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

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

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

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

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

As of March 18, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to maintain this pace and delays or setbacks are possible in the future, including where a pre-approval inspection or an inspection of clinical sites is required and, due to the COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspection during the review period. In 2020, several companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may similarly experience delays in their regulatory activities due to the COVID-19 pandemic.

In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. For example, regulatory agencies may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. Regulators may approve a product candidate for a smaller patient population (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 or use of different manufacturing facilities) than we are seeking. If we are delayed in obtaining or unable to obtain necessary regulatory approvals, or if we obtain more limited regulatory approvals than we expect, our business, prospects, financial condition and results of operations may suffer.

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

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

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

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

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

Even if we obtain and maintain approval for our product candidates in one jurisdiction, we may never obtain approval for our product candidates in other jurisdictions, which would limit our market opportunities and adversely affect our business.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by the EMA or other regulatory authorities in other countries or jurisdictions, and approval by the EMA or another regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. For example, though we received standard marketing authorization of Libmeldy (OTL-200) from the European Commission in December 2020, there is no guarantee that we will receive approval from the FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit an MAA to the EMA for approval of our product candidates in the European Union but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects 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), however there was an initial transition period during which European Union medicines legislation continued to apply in the United Kingdom. This transition period ended on December 31, 2020 but United Kingdom and the European Union have signed a EU-UK Trade and Cooperation Agreement (the "TCA"), which became provisionally applicable on January 1, 2021 and will become formally applicable once ratified by both the United Kingdom and the European Union. Under the terms of the TCA, the European Union and Great Britain have separate regulatory regimes for pharmaceutical products, although there are some provisions for mutual recognition of standards, for example with regards to GMP. For instance, Great Britain will now no longer be covered by the centralized procedure for obtaining EEA-wide marketing authorizations for medicinal products (under the Northern Irish Protocol, centralized marketing authorizations will continue to be recognized in Northern Ireland) and a separate process for authorization of medicinal products will be required, resulting in an authorization covering the United Kingdom or Great Britain only. 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.

Most of the clinical trials for our product candidates conducted to date were conducted at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

To date, most of the clinical trials conducted on our product candidates have been conducted outside the United States. For example, we do not yet have an IND open in the United States for OTL-203 for MPS-IH or OTL-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, as noted in the risk factor immediately above. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, due to study design or otherwise, it would likely result in the need for additional

trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates. Further, without an IND open in the United States, we forego more frequent interactions and dialogue with FDA regarding the design and conduct of our trials as well as product comparability, which may delay or halt the development of our product candidates later in development should FDA later disagree with the design or conduct of our trials or product comparability approach.

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

While we intend to seek designations for our product candidates with the FDA and 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-200 for MLD and OTL-103 for WAS received RMAT designation from the FDA and both OTL-300 for TDT and OTL-203 for MPS-IH received a Priority Medicines, or PRIME, designation from EMA. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

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

In addition, we may seek RMAT designation for some of our other product candidates. An RMAT is defined as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. The RMAT program is intended to facilitate efficient development and expedite review of RMATs, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. A BLA for an RMAT may be eligible for priority review or accelerated approval. An RMAT may be eligible for priority review if it treats a serious condition, and, if approved would provide a significant improvement in the safety or effectiveness of the treatment of the condition. An RMAT may be eligible for accelerated approval through (1) surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit or (2) reliance upon data obtained from a meaningful number of sites. Benefits of such designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real-world evidence, such as electronic health records, the collection of larger confirmatory data sets, or post-approval monitoring of all patients treated with such therapy prior to its approval. RMAT designation is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a RMAT, the FDA may disagree and instead determine not to make

such designation. In any event, the receipt of RMAT designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as for RMAT designation, the FDA may later decide that the biological products no longer meet the conditions for qualification.

In addition, the FDA has granted Rare Pediatric Disease designation to Strimvelis, OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS, OTL-201 for MPS-IIIA and OTL-203 for MPS-IH, and we may seek Rare Pediatric Disease designation for some of our other product candidates. The FDA defines a "rare pediatric disease" as a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making in the U.S. a drug for such disease or condition will be received from sales in the U.S. of such drug. Under the FDA's Rare Pediatric Disease Priority Review Voucher, or PRV, program, upon the approval of a BLA for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for a Rare Pediatric Disease PRV that can be used to obtain priority review for a subsequent new drug application or BLA. The PRV may be sold or transferred an unlimited number of times. Congress has extended the PRV program through September 30, 2024, with potential for PRVs to be granted through September 30, 2026. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for Libmeldy (OTL-200), OTL-101 for ADA-SCID, OTL-103 for WAS, OTL-201 for MPS-IIIA and OTL-203 for MPS-IH and qualify for such a PRV, the program may no longer be in effect at the time or the value of any such PRV may decrease such that we are may not be able to realize the benefits of such PRV.

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

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

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

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

We have sought and received orphan drug designation for Libmeldy (OTL-200), OTL-101 for ADA-SCID, OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-IIIA from the FDA and EMA, for OTL-203 for MPS-IH from the FDA, and for OTL-300 for TDT from the EMA, but we may be unable to obtain orphan drug designation for our other product candidates, and, even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales

in the United States. In the EEA, 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 EEA. 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 EEA would be sufficient to justify the necessary investment in developing the drug or biologic product. In either case, the applicant for orphan designation must also demonstrate that no satisfactory method of diagnosis, prevention, or treatment for the condition has been authorized (or, if a method exists, the new product would be a significant benefit to those affected compared to the product available).

We have sought and received orphan drug designation for Libmeldy, OTL-101 for ADA-SCID, OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-IIIA from the FDA and EMA, for OTL-203 for MPS-IH from the FDA, and for OTL-300 for TDT from the EMA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our 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 EEA. The exclusivity period in the EEA 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 EEA, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

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

We may seek a conditional marketing authorization in Europe for some or all of our current product candidates, but we may not be able to obtain or maintain such designation.

As part of its marketing authorization process, the EMA may grant marketing authorizations for certain categories of medicinal products on the basis of less complete data than is normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required or in the interests of public health. In such cases, it is possible for the CHMP to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating or life-threatening diseases and those designated as orphan medicinal products.

A conditional marketing authorization may be granted when the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data post-authorization;
- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data is still required.

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

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

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

Libmeldy, Strimvelis and any of our product candidates for which we obtain regulatory approval will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. For example, as a post-marketing commitment, we are continuing to follow patients in the OTL-200 clinical development program for up to 15 years, and data will be presented to regulators at agreed points in order to further characterize the long-term efficacy and safety of Libmeldy, particularly in the early symptomatic early juvenile population. For an example of adverse event reporting, in October 2020 we notified the EMA and relevant local European regulatory authorities after we became aware that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with leukemia.

Any regulatory approvals that we receive for our product candidates also may be subject to a REMS or equivalent requirement from a non-U.S. regulatory authority, limitations on the approved indicated uses for which the product may be marketed or to the

conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, in the United States, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo long-term safety and efficacy follow-up for as long as 15 years post therapy. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In the 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.

Risks related to manufacturing and supply

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience, and we rely on third party manufacturers that are often our single source of supply. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial products or our product candidates or otherwise harm our business.

Biological products are inherently difficult to manufacture, and gene therapy products are complex biological products, the development and manufacture of which necessitates substantial expertise and capital investment. Libmeldy, Strimvelis and our product candidates are individually manufactured for each patient using complex processes in specialized facilities. Our production process requires a variety of raw materials, some of which are highly specialized, including the viral vector that encodes for the functional copy of the missing or faulty gene to treat a specific disease. Some of these raw materials have limited and, in some cases, sole suppliers. Even though we plan to have back-up supplies of raw materials whenever possible, we cannot be certain such supplies will be sufficient if our primary sources are unavailable. A shortage of a critical raw material or a technical issue during manufacturing may lead to delays in clinical development or commercialization of our product candidates. Additionally, each manufacturing batch must meet certain analytical specifications to be released and production difficulties caused by unforeseen events may delay the availability of one or more of the necessary raw materials or delay the manufacture of our product candidates for use in clinical trials or for commercial supply. As a result of the COVID-19 global pandemic, some of our CDMOs have experienced, and may continue to experience, delays and other direct impacts at their manufacturing sites as a result of travel restrictions, shelter-in-place policies or restrictions and other disruptions caused by the pandemic.

We have contracted with third party CDMOs for the manufacture of our viral vectors and drug product. We expect these CDMOs will be capable of providing sufficient quantities of our viral vectors and gene therapy products to meet the anticipated scale of our clinical trials and current and initial commercial demands, if any additional products are approved. However, to meet our projected needs for further commercial manufacturing and clinical trials of new product candidates, third parties with whom we currently work might need to increase their scale and frequency of production or we will need to secure alternate suppliers or develop in-house capabilities. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements; however, identifying and establishing relationships with such sources, if necessary, could result in significant delays or material additional costs, which could delay or prevent the development of our product candidates and would have a negative impact on our business, financial condition and results of operations.

Additionally, the manufacturers of pharmaceutical products must comply with strictly enforced cGMP requirements, state and federal regulations, as well as foreign requirements when applicable. Any failure of our CDMOs to adhere to or document compliance to such regulatory requirements could lead to a delay or interruption in the availability of our program materials for clinical trials. If our manufacturers were to fail to comply with the FDA, EMA, or other regulatory authority, it could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of raw materials, product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. Our dependence upon others for the manufacture of our gene therapies may also adversely affect our future profit margins and our ability to commercialize any product candidates that receive regulatory approval on a timely and competitive basis.

Delays in obtaining regulatory approval of our or our CDMOs' manufacturing process and facility or disruptions in our manufacturing process may delay or disrupt our commercialization efforts. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product.

Before we can begin to commercially manufacture our viral vector or product candidates in a CDMO facility, we must obtain regulatory approval from the FDA for our manufacturing processes and for the facility in which manufacturing is performed. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product; therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our CDMOs manufacturing facility by the FDA and other relevant regulatory authorities before any of our gene therapy product candidates can obtain marketing approval.

Since March 2020, when foreign and domestic inspections were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. The FDA has developed a rating system to assist in determining when and where it is safest to conduct prioritized domestic inspections and resumed inspections in China and India in early 2021. In April 2021, the FDA issued guidance formally announcing plans to employ remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Should the FDA determine that a manufacturing or bioresearch monitoring inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be appropriate, the agency has stated that it generally intends to issue a complete response letter. Further, if there is inadequate information to make a determination on the acceptability of a facility, the FDA may defer action on the application until an inspection can be completed. In 2020, several companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities.

In order to obtain approval, we will need to ensure that all of our processes, quality systems, methods, equipment, policies and procedures are compliant with cGMP, and perform extensive audits of vendors, contract laboratories, CDMOs and suppliers. If any of our vendors, contract laboratories, CDMOs or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to spend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs.

We do not have experience as a company managing a complex supply chain or satisfying manufacturing-related regulatory requirements.

The FDA, EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, EMA or other foreign regulatory authorities may require that we not distribute a product lot until the relevant agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in a viral vector or a gene therapy product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results

of operations and prospects. Problems in our manufacturing processes could restrict our ability to meet market demand for our products.

Managing an autologous ex vivo gene therapy supply chain is highly complex. We must identify, engage, and coordinate with treatment centers where patients' cellular source material must be collected, prepared, stored and transported to the manufacturing facility and the cryopreserved drug product must be returned to the treatment center for administration into the patient using controlled temperature shipping containers.

Once collected from the patient, the cellular source material must be prepared and stored according to specified procedures. While we intend to standardize the processes at treatment centers, if there is a deviation of the processes, the cellular source material from a patient could be adversely impacted and potentially result in manufacturing failures. The 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 and processed within three days of collection. While we intend to use reputable couriers and agents for the transport of such materials, if the shipping container is opened or damaged such that the cool temperature is not maintained, the cellular source material may be adversely impacted and it may not be feasible to manufacture a drug product for the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, being held up at a customs point, COVID-19 impacts or other events, the cellular source material may not be delivered within a time window that will allow for its use for the successful manufacture of a drug product.

Similarly, the patient's autologous drug product must be returned to the clinical site for administration into the patient using a specialized shipping container that maintains the material at a very low temperature for a period of typically up to ten days. While we intend to use reputable couriers and agents for the transport of our drug products, if the shipping container is opened or damaged such that the very low temperature is not maintained, the drug product may be adversely impacted and it may not be feasible to administer it to the patient or, if administered, it could cause harm to the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, being held up at a customs point, COVID-19 impacts or other events, and is not delivered to the clinical site within the time period that the very low temperature is maintained, the drug product may be adversely affected and be unable to be administered or, if administered, could cause harm to the patient.

We may be delayed or unable to identify, engage, successfully coordinate or qualify with treatment centers in the regions we are targeting as part of our commercial launch strategy, which could delay or prevent patients from receiving gene therapy treatments, if approved. For example, due to COVID-19-related travel restrictions, some in-person visits to qualify certain potential treatment centers were postponed or required to take place remotely. If our treatment centers fail to perform satisfactorily, we may suffer reputational, operational, and business harm.

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

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

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

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

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

Some of the raw materials required in our manufacturing processes are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our vectors or drug product could adversely impact or disrupt the commercial

manufacturing or the production of clinical material, which could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Interruptions in the supply of viral vectors 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, due to transportation or other delays, including delays or disruptions resulting from the impact of the COVID-19 pandemic, or the loss thereof could hinder our ability to timely distribute our products and satisfy customer demand. Any unforeseen failure in the storage of the viral vectors or drug products or loss in supply could delay our clinical trials and result in a loss of our market share for our commercial products or our product candidates, if approved, and negatively affect our business, financial condition, results of operations and prospects.

Our cryopreserved product candidates require specific storage, handling and administration at the clinical sites.

Our cryopreserved product candidates must be stored at very low temperatures in specialized freezers or specialized shipping containers until immediately prior to use. For administration, the cryopreserved drug product container must be carefully removed from storage, and rapidly thawed under controlled temperature conditions in an area proximal to the patient's bedside and administered into the patient. The handling, thawing and administration of the cryopreserved gene therapy product must be performed according to specific instructions, typically using specific disposables and in some steps within specific time periods. Failure to correctly handle the product, follow the instructions for thawing and administration and or failure to administer the product within the specified period post-thaw could negatively impact the efficacy and or safety of the product.

Risks related to our reliance on third parties

We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialize product candidates. If these collaborations are not successful, our business could be adversely affected.

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

We 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 Quarterly 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 will likely be time-consuming and complex. Our ability to reach a definitive collaboration agreement in such instances will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of several factors. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

We utilize, and expect to continue to utilize, third parties to conduct some or all aspects of our vector production and product manufacturing for the foreseeable future, and these third parties may not perform satisfactorily.

We are not able to independently manufacture material for our planned clinical programs or our commercial supply of Libmeldy, Strimvelis or any other product for which we obtain marketing approval, if any, and we do not expect to be able to in the foreseeable future. We currently rely on our CDMOs and in some cases academic partners for the production of our viral vectors and product candidates for our ongoing registrational and clinical trials and preclinical studies. For future clinical trials and for Libmeldy and other products for which we obtain marketing approval, if any, we intend to utilize materials manufactured by CDMOs. If our academic partners or these CDMOs do not successfully carry out their contractual duties, meet expected deadlines or manufacture our viral vector and product candidates in accordance with regulatory requirements or if there are disagreements between us and our academic partners or these CDMOs, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support approval of our product candidates or the FDA, EMA or other regulatory agencies may refuse to accept our clinical or preclinical data. In such instances, we may need to enter into an appropriate third-party relationship, which may not be readily available or available on acceptable terms. This could cause additional delay or increased expense prior to the approval of our product candidates and could have a negative impact on our business, financial condition, results of operations and prospects.

We partner with CDMOs and intend to utilize viral vectors and gene therapy products manufactured by CDMOs for our future clinical trials and products for which we obtain marketing approval. In some cases, we may need to perform clinical or analytical or other animal or cell-based testing to demonstrate that materials produced by these CDMOs, or any other third-party manufacturer that we engage, is comparable to the material produced by our academic partners and utilized in our registrational and clinical trials of our product candidates. There is no assurance that these CDMOs, or any other future third-party manufacturer that we engage, will be successful in producing any or all of our viral vector or product candidates, that any such product will, if required, pass the required comparability testing, or that any materials produced by these CDMOs or any other third-party manufacturer that we engage will have the same effect in patients that we have observed to date with respect to materials produced by our academic partners. We believe that our manufacturing network will have sufficient capacity to meet demand for our clinical and existing and expected initial commercial needs, but there is a risk that if supplies are interrupted or result in poor yield or quality, it would materially harm our business. Additionally, if the gene therapy industry were to grow, we may encounter increasing competition for the raw materials and consumables necessary to produce our product candidates. Furthermore, demand for CDMO cGMP manufacturing capabilities may grow at a faster rate than existing manufacturing capacity, which could disrupt our ability to find and retain third-party manufacturers capable of producing sufficient quantities of our viral vectors or product candidates for future clinical trials or to meet expected initial commercial demand.

Under certain circumstances, our current CDMOs may terminate their engagements with us. If we need to enter into alternative arrangements, it could delay our development activities. Our reliance on our CDMOs for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations.

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

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider or the COVID-19 global pandemic or similar future pandemics or disruptions.

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

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

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

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

We do not control the design or conduct of the academic-sponsored trials, and it is possible that the FDA or EMA will not view these academic-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. Such arrangements provide us certain information rights with respect to the academic-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the academic-sponsored trials. However, we do not have control over the timing and reporting of the data from academic-sponsored trials, nor do we own the data from the academic-sponsored trials. If we are unable to confirm or replicate the results from the academic-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of OTL-102 for X-CGD, OTL-203 for MPS-IH, OTL-201 for MPS-IIIA or any other product candidate investigated in an academic-sponsored clinical trial. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates or if the data proves to be inadequate compared to the first-hand knowledge we might have gained had the academic-

sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

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

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

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

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

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

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

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

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

We currently depend on a limited number of suppliers and, in some instances, a sole supplier, for some of the components and equipment necessary for the production of our viral vectors and drug product. We cannot be sure that these suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a sole or a limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components, and, in some cases, no alternatives. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. As a result of the COVID-19 pandemic, we may experience

supply shortages from some of our suppliers. Any disruption in supply from any supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we are required to switch to a replacement supplier, the manufacture and delivery of our viral vectors and product candidates could be interrupted for an extended period, adversely affecting our business. Establishing additional or replacement suppliers may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. For example, the FDA or EMA could require additional supplemental data, manufacturing data and comparability data up to and including clinical trial data if we rely upon a new supplier. While we seek to maintain adequate inventory of the components and materials used in our product candidates, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to conduct our clinical trials and, if our product candidates are approved, to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, the FDA must review and approve the individual components of our production process, which includes raw materials, the manufacturing processes and facilities of our suppliers. Some of our current suppliers have not undergone this process nor have they had any components included in any product approved by the FDA.

Our reliance on these suppliers subjects us to a number of risks that could harm our reputation, business, and financial condition, including, among other things:

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers;
- interruptions, shortages, delivery delays and potential discontinuation of supply as a result of the ongoing COVID-19 global pandemic, or any recurrence of the pandemic or future pandemics; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, costs could significantly increase and our ability to conduct our clinical trials and, if our product candidates are approved, to meet demand for our products could be impacted.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we currently rely on third parties to manufacture our vectors and our commercial products and product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy approach, we must, at times, share trade secrets with such third parties. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets.

Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are

notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to commercialization of our product candidates

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

We intend to commercialize our product candidates, if approved, in the United States, Europe, and other markets, and we are currently undertaking preparations for our commercial launch of Libmeldy in Europe. We intend to commercialize Libmeldy and our other product candidates, if approved, directly with specialized teams, given the relative rarity of the indications we are targeting. Although we have substantially built out our initial commercial infrastructure in preparation for our commercial launch of Libmeldy in Europe, we are continuing to build out our commercial capabilities and infrastructure and have a limited marketing and sales team for the marketing, sales and distribution of Strimvelis, Libmeldy and our product candidates, if approved. In order to commercialize Libmeldy, Strimvelis, if sales resume, and OTL-103 for WAS, if approved, or any of our other product candidates that may be approved, we must continue to build and expand, on a territory-by-territory basis, marketing, sales, distribution, managerial and other capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If we are unable to establish sufficient commercial capabilities and infrastructure, we may be unable to generate sufficient revenue to sustain our business.

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 Libmeldy and our product candidates, if approved, 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;
- changes or setbacks at treatment centers contracted for the administration of any approved treatments;
- the occurrence of adverse events;
- 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.

In addition, we will need to commit significant additional management and other resources to maintain and grow our sales organization. We may not be able to achieve the necessary development and growth in a cost-effective manner or realize a positive return on our investment.

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, sell and gain reimbursement for Libmeldy and any of our product candidates for which we obtain marketing approval, we will be unable to generate any product revenue.

To successfully commercialize Libmeldy and 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 marketing capabilities is, and will continue to be, expensive and time-consuming and could delay any product launch, including our planned launch of Libmeldy in Europe in the first half of 2021. 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.

We face significant competition in our industry and there can be no assurance that our commercial products or our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.

We operate in a highly competitive segment of the biopharmaceutical market. We face competition from many different sources, including larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies, some of which are being marketed by large and international companies. In addition, we expect to compete with new treatments that are under development or may be advanced into the clinic by our competitors. There are a variety of product candidates, including gene therapies, in development for the indications that we are targeting, including new areas that we may target as part of our strategic initiatives.

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

Many of our competitors have significantly greater financial, product candidate development, manufacturing and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for their products, and mergers and acquisitions within these industries may result in even more resources being concentrated among a smaller number of larger competitors. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our business would be materially and adversely affected if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, have broader market acceptance, are more convenient or are less expensive than any product candidate that we may develop.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing

methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

If the size and value of the market opportunities for our commercial products or product candidates are smaller than our estimates, or if we have difficulty in finding patients that meet eligibility requirements for Libmeldy, Strimvelis or any of our product candidates, if approved, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for immunological disorders and inherited neurometabolic and neurodegenerative genetic disorders. We base our market opportunity estimates on a variety of factors, including our estimates of the number of people who have these diseases, the potential scope of our approved product labels, the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, various pricing scenarios, and our understanding of reimbursement policies for rare diseases in particular countries. These estimates are based on many assumptions and may prove to be incorrect, and new studies may reduce the estimated incidence or prevalence of these diseases. Estimating market opportunities can be particularly challenging for ultra-rare indications, such as the ones we currently address, as epidemiological data is often more limited than for more prevalent indications and can require additional assumptions to assess potential patient populations. For example, as we advance our product candidates towards commercialization, learn more about market dynamics and engage with regulators on potential marketing approvals, our view of the initial potential market opportunity for our products will become more refined. In some cases, the approved label may initially be directed to a narrower patient population with the opportunity to expand the label upon submission of additional clinical data. For example, in the case of Libmeldy, we are now initially focused primarily on annual incidence of the disease, and in the case of OTL-103 for WAS we are initially focused primarily on prevalence of the disease. In each case this means the initial market opportunity for these product candidates may be smaller than the total addressable market opportunity that could be achieved over time. If we are unable to advance product candidates with attractive market opportunities, our future product revenues may be smaller than anticipated and our business may suffer. Patient identification efforts also influence the ability to address a patient population. If efforts in patient identification are unsuccessful or less impactful than anticipated, for instance, because of a lack of newborn screening or diagnostic initiatives, inadequate disease awareness among healthcare providers, or otherwise, we may not address the entirety of the opportunity we are seeking. As a result, patients may be difficult to identify and access, the addressable patient population in the United States, Europe and elsewhere may turn out to be lower than expected, or patients may not be otherwise amenable to treatment with our products, all of which would adversely affect our business, financial condition, results of operations and prospects.

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

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

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

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

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

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

We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, if approved. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a payor not to cover our gene therapies could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about coverage and reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow the CMS to a substantial degree. It is difficult to predict what the CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Factors payors consider in determining reimbursement are based on whether the product is:

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

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

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

procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

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

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

Risks related to the impact of COVID-19

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

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

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

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

- the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, hospitals or academic centers serving as our clinical trial sites and staff supporting the conduct of our clinical trials;
- limitations on travel that could interrupt treatment center qualification, key trial activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that may impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials;
- interruption in global shipping affecting the transport of clinical trial materials, such as patient samples, investigational drug product and conditioning drugs and other supplies used in our clinical trials;

- business disruptions caused by potential workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments and operations, disruptions or delays in subleasing any leased facilities no longer required for our business operations, staffing shortages, travel limitations or mass transit disruptions, any of which could adversely impact our business operations or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors;
- business disruptions involving our third parties on whom we rely, including CROs and other collaborators for the conduct of our clinical trials or our third-party suppliers or CDMOs, which could impact their ability to perform adequately or disrupt our supply chain; and
- changes in hospital or research institution policies or government regulations, which could delay or adversely impact our ability to conduct our clinical trials.

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

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

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

The extent to which the COVID-19 pandemic impacts our business, and our clinical development and regulatory efforts, as well as our supply chain, will depend on future developments that are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the outbreak, government actions, such as travel restrictions, quarantines and social distancing requirements in the U.S. and in other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and in other countries to contain and treat the disease. Accordingly, we do not yet know the full extent of potential delays or impacts on our business, our clinical and regulatory activities, our research programs, healthcare systems or the global economy as a whole. However, these effects could materially and adversely affect our business, financial condition, results of operations and growth prospects, which may in turn also have the effect of heightening many of the other risks and uncertainties described elsewhere in this “Risk Factors” section.

Risks related to our business operations

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology, with only a limited number of gene therapy products approved to date. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. 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. 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. This could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

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

We acquired worldwide rights to Libmeldy (OTL-200), Strimvelis, 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-IH 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. For example, in May 2020, we announced a reduction of the investment in and scope of our OTL-101 and OTL-300 programs and, based on the reallocation of capital, we have determined to prioritize other programs, including research and development projects in less rare indications. 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 Libmeldy, Strimvelis, OTL-103 for WAS, OTL-203 for MPS-IH and OTL-300 for TDT, or any future acquisitions, license arrangements or other strategic transactions related to our current or future product candidates could harm our business. Financial aspects of such future transactions that could alter our financial position, or operating results include:

- use of cash resources;
- higher than anticipated acquisition costs and expenses;
- potentially dilutive issuances of equity securities;

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

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

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

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

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of Libmeldy, Strimvelis or 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 and planned sales of Libmeldy or any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. For example, in October 2020, we were notified that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with leukemia. Subsequent findings confirmed that the patient's leukemia was due to insertional oncogenesis attributable to treatment with Strimvelis, though the CHMP concluded that the risk-benefit balance remains favorable. If we cannot successfully defend against product liability claims, including any claims related to treatment with Strimvelis, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

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

We believe our product liability insurance coverage is sufficient in light of our current commercial and clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage each time we commercialize an additional product, but we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could adversely affect our results of operations and business.

Patients with the diseases targeted by certain of our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life- threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

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.

Security incidents have become more prevalent across industries and may occur on our systems or on the systems of our third parties service providers. These security incidents may be caused by or result in but are not limited to security breaches, computer malware or malicious software, ransomware, computer hacking, denial of service attacks, security system control failures in our own systems or from service providers we use, email phishing, software vulnerabilities, social engineering, sabotage, drive-by downloads and the malfeasance of our or our service providers' employees. Although we have taken a number of measures to detect, effectively remediate and prevent future phishing and other attacks and security threats, we cannot be certain that our efforts will be effective.

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. The ongoing COVID-19 pandemic and the related disruptions to our business and our collaborators', contractors' and consultants' businesses may increase the risk of cyberattacks. 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.

Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team and key employees, including our Chief Executive Officer and our President & Chief Operating Officer, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We do not maintain "key person" insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives.

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

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

In May 2020, we undertook an organizational restructuring that reduced our workforce by approximately 25%, including the closure of our Menlo Park, California office. We also decided to discontinue building out our leased manufacturing facility in Fremont, California, despite having devoted costs and resources to the project, which may not be recouped, and despite incurring wind down costs associated with abandoning the construction. We have recorded $5.7 million in non-cash impairment charges associated with the Fremont operating lease right-of-use asset, design costs classified as construction-in-process, and laboratory equipment at our Menlo Park facility. In December 2020, we entered into a sublease agreement with an unrelated third-party whereby we subleased the entire Fremont facility to such third party. The sublease is for the entire remaining term of lease.

Future growth would impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. Due to our limited resources, we may not be able to effectively manage our operations or recruit and retain qualified personnel, which may result in weaknesses in our infrastructure and operations, risks that we may not be able to comply with legal and regulatory requirements, and loss of employees and reduced productivity among remaining employees. For example, the workforce reduction may negatively impact our clinical, regulatory, technical operations, and commercial functions, which would have a negative impact on our ability to successfully develop, and ultimately, commercialize our product candidates. Our future financial performance and our ability to develop our product candidates or additional assets will depend, in part, on our ability to effectively manage any future growth or restructuring, as the case may be.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners, CROs and CDMOs. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Misconduct by these parties could include intentional failures to (i) comply with the regulations of the FDA, EMA or of other foreign regulatory authorities, (ii) provide accurate information to the FDA, EMA and other foreign regulatory authorities, (iii) comply with healthcare fraud and abuse laws and regulations in the United States and abroad, (iv) report financial information or data accurately or (v) disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions such as criminal and administrative penalties, damages, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of noncompliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

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

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

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

In December 2018, a federal district court in Texas ruled the individual mandate is a critical and inseverable feature of the ACA. Since the individual mandate was repealed as part of the Tax Act, the court held that the remaining provisions of the ACA were also invalid. In December 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate was unconstitutional and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. In March 2020, the United States Supreme Court granted the petitions for writs of certiorari to review the case, and the Supreme Court held oral arguments in November 2020. The Court has not rendered its opinion for such case and the ACA remains in effect. It is unclear what effect these developments will have on the status of the ACA.

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

There have also been several attempts to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. For example, former President Trump signed an Executive Order that terminated the cost-sharing subsidies that reimburse insurers under the ACA until Congress made necessary appropriations for such subsidies. However, in August 2020 the U.S. Court of Appeals ruled in two separate cases that the federal government was liable for the full amount of unpaid cost sharing reduction payments for the years preceding and including 2017. For unpaid amounts for 2018 and later, additional litigation will be required to determine the amounts due, if any.

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

Congress could consider subsequent legislation to replace elements of the ACA that are repealed, invalidated or not implemented. 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.

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

In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several 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. 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. In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain health care facilities. For 2019 and 2018, CMS altered the reimbursement formula on specified covered outpatient drugs, which was challenged in court. Most recently, in July 2020, the U.S. Court of Appeals for the District of Columbia held that the changes were within CMS's authority. It is unclear how these developments could affect covered hospitals who might purchase our future products and the rates we may charge such facilities for our approved products in the future, if any.

There have been several other actions taken at a federal level seeking to lower drug prices. For example, the FDA released a final rule, which went into effect in November 2020, providing guidance for states to build and submit importation plans for drugs from Canada. In November 2020, CMS also issued an Interim Final Rule implementing the Most Favored Nation model under which Medicare Part B reimbursement rates would be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. However, the Most Favored Nation model has not been implemented because the U.S. District Court for the Northern District of California issued a nationwide preliminary injunction in December 2020 pending completion of notice-and-comment procedures under the Administrative Procedure Act. In January 2021, in a separate lawsuit brought by industry groups in the U.S. District of Maryland, the government defendants entered a joint motion to stay litigation on the condition that the government would not appeal the preliminary injunction granted in the U.S. District Court for the Northern District of California and that performance for any final regulation stemming from the MFN Interim Final Rule shall not commence earlier than 60 days after publication of that regulation in the Federal Register. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada and the MFN Model may materially and adversely affect the price we receive for any of our product candidates. Although President Biden and his administration may reverse or otherwise change these measures, Congress has indicated that it will continue to seek new legislative measures to control drug costs.

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

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

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

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

We are subject to the UK Bribery Act 2010, or the Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, and other anti-corruption laws, as well as export control laws, import and customs laws, trade and economic sanctions laws and other laws governing our operations.

Our operations are subject to anti-corruption laws, including the Bribery Act, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions and embargoes on certain countries and persons, anti-money laundering laws, import and customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws health information privacy and security laws, and other health care laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to, the below:

- The federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties.
- The federal civil and criminal false claims laws and civil monetary penalty laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government or

knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery.

- The anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program.
- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.
- The U.S. federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.
- The federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs.
- The federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- Many states in the United States have enacted laws that regulate the privacy and/or security of certain types of personal information. For example, in California the California Consumer Protection Act (CCPA), which went into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. After a delay, the CCPA became subject to enforcement as of July 1, 2020. Although clinical trial data and protected health information subject to HIPAA are currently exempt from CCPA, we may be subject to the CCPA with respect to other personal information regarding California residents. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.
- Additionally, a new California ballot initiative, the California Privacy Rights Act, or "CPRA," was passed in November 2020. Effective starting on January 1, 2023, the CPRA imposes additional obligations on companies covered by the legislation and will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement

and enforce the CCPA and the CPRA. The effects of the CCPA and the CPRA are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement and/or litigation.

- Certain other state laws impose similar privacy obligations, and we also expect anticipate that more states to may enact legislation similar to the CCPA, which provides consumers with new privacy rights and increases the privacy and security obligations of entities handling certain personal information of such consumers. The CCPA has prompted a number of proposals for new federal and state-level privacy legislation. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs and/or changes in business practices and policies.

Recent events in the UK may further complicate our data protection compliance efforts in Europe. Following the UK's withdrawal from the EU on January 31, 2020 and the end of the transitional arrangements agreed between the UK and EU, as of January 1, 2021, the GDPR has been incorporated into UK domestic law by virtue of section 3 of the European Union (Withdrawal) Act 2018 and amended by the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019. UK-based organizations doing business in the EU will need to continue to comply with the EU General Data Protection Regulation ("GDPR"). Further, there is uncertainty with regard to how data transfers to and from the UK will be regulated. Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute and False Claims Act and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the GDPR, which became effective May 2018 also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. There are ambiguities as to what is required to comply with these state requirements, and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

In the event we decide to conduct clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, including personal health data, is subject to the GDPR. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, 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 €20.0 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. In addition, further to the United Kingdom's exit from the EU ("Brexit") on January 31, 2020 and the expiry of the subsequent transition period on December 31, 2020, the GDPR has been brought into UK law as the "UK GDPR", but there may be further developments about the regulation of particular issues such as UK-EU data transfers. A bridging mechanism is currently in place between the UK and the EU to enable the free flow of data until an adequacy decision by the European Commission regarding the UK can be put in place. However, if we engage in personal data processing activities that cause us to be subject to UK data protection law, we may be required to take steps to ensure the lawfulness of our data transfers in the future.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge and may not comply under one or more of such laws, regulations, and

guidance. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive share options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

If we or our CDMOs and CROs fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We and third parties such as our CDMOs and CROs are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

As a company based outside of the United States, our business is subject to economic, political, regulatory and other risks associated with international operations.

As a company based partly in the United Kingdom and EU countries, our business is subject to risks associated with conducting business outside of the United States. Many of our suppliers and clinical trial relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in the United Kingdom and other non-U.S. economies and markets, including the substantial economic dislocation that has occurred and is likely to persist as a result of the impact of the COVID-19 global pandemic;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;

- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the eligible members of the UK electorate for the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws or practice;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, fires and public health epidemics and pandemics, including the current COVID-19 global pandemic.

Risks related to our intellectual property

We may become subject to claims that we are infringing certain third-party patents, for example, patents relating to lentiviral vectors, or other third-party intellectual property rights, any of which may prevent or delay our development and commercialization efforts and have a material adverse effect on our business.

Our commercial success depends in part on avoiding infringing, misappropriating and otherwise violating the patents and other intellectual property and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, and administrative proceedings such as interferences, *inter partes* review and post grant review proceedings before the U.S. Patent and Trademark Office, or USPTO, and opposition proceedings before foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned or controlled by third parties, including our competitors, exist in the fields in which we are pursuing products and product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our products and product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we or our licensors are employing their proprietary technology without authorization. There may be third party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment relating to our products and product candidates and, because patent applications can take many years to issue, there may be currently pending third party patent applications which may later result in issued patents, in each case that our products and product candidates, their manufacture or use may infringe or be alleged to infringe.

Parties making patent infringement claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our products or product candidates. Defense of these claims, including demonstrating non-infringement, invalidity or unenforceability of the respective patent rights in question, regardless of their merit, is time-consuming, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. For example, in order to successfully challenge the validity of any U.S. patent in federal court, we would need to overcome a presumption of validity. This is a high burden requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, and we can provide no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. We may not have sufficient resources to bring these actions to a successful conclusion. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments.

In the event that a holder of any such patents seeks to enforce its patent rights against us with respect to one or more of our products or product candidates, and our defenses against the infringement of such patent rights are unsuccessful, we may be precluded from commercializing such products and product candidates, even if approved, without first obtaining a license to some or all of these patents, which may not be available on commercially reasonable terms or at all. Moreover, we may be required to pay significant fees and royalties to secure a license to the applicable patents. Such a license may only be non-exclusive, in which case our ability to stop

others from using or commercializing technology and products similar or identical to ours may be limited. Furthermore, we could be liable for damages to the holders of these patents, which may be significant and could include treble damages if we are found to have willfully infringed such patents. In the event that a challenge to these patents were to be unsuccessful or we were to become subject to litigation or unable to obtain a license on commercially reasonable terms with respect to these patents, it could harm our business, financial condition, results of operations and prospects.

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

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

In addition, our trade secrets may otherwise become known or be independently discovered by competitors. Competitors and other third parties could purchase our products and product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe, misappropriate or otherwise violate our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If our trade secrets are not adequately protected or sufficient to provide an advantage over our competitors, our competitive position could be adversely affected, as could our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets.

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

We are highly dependent on the intellectual property and data licensed to us by third parties that are important or necessary to the development of our technology and products and product candidates, including technology related to the manufacture and use of our products and product candidates. In particular, we do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis, Libmeldy or any of our lead product candidates. We have in-licensed 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, Libmeldy, and OTL-300 for TDT, certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-IH, and certain other intellectual property for our clinical and preclinical programs. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

Although our license rights from The Regents of the University of California, University College London, GSK, and Telethon-OSR, are exclusive, they are limited to particular fields, such as 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 particular licensor may have the right to terminate such agreements. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected products and product candidates. Termination of our license agreements or reduction or elimination of our rights under them may result in our having to negotiate a new or reinstated agreement, which may not be available to us on equally favorable terms, or at all, which may mean we are unable to develop or commercialize the affected product or product candidate or cause us to lose our rights under the agreement. Any of the foregoing could have a material adverse effect on our business.

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

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. We currently do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis, Libmeldy or OTL-103. Many of our products and product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all. Our or our licensors' failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties, in particular, other established and better-financed gene therapy companies having established development,

manufacturing and distribution capabilities, to make competing products or impact our ability to develop, manufacture and market our products and product candidates, even if approved, on a commercially viable basis, if at all, which could have a material adverse effect on our business.

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

We currently do not own any issued patents related to Strimvelis, Libmeldy or our lead product candidates. Certain intellectual property related to Strimvelis, Libmeldy and all of our product candidates are in-licensed from third parties, but we have not in-licensed any issued patents related to Strimvelis, Libmeldy or any of our product candidates, except for OTL-101 for which we have in-licensed a U.S. patent and its counterpart European patent from The Regents of the University of California and University College London, respectively. In certain situations and as considered appropriate, we and our licensors have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States relating to current and future products and product candidates that are important to our business. However, we cannot predict whether the patent applications currently being pursued will issue as patents, whether the claims of any resulting patents will provide us with a competitive advantage or prevent competitors from designing around our claims to develop competing technologies in a non-infringing manner, or whether we will be able to successfully pursue patent applications in the future relating to our current or future products and product candidates. Moreover, the patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Furthermore, we, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to seek additional patent protection.

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

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

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

Filing, prosecuting, maintaining, defending and enforcing patents on products and product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. There can be no assurance that we will obtain or maintain patent rights in or outside the United States under any future license agreements. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States even in jurisdictions where we and our licensors pursue patent protection. Consequently, we and our licensors may not be able to prevent third parties from practicing our inventions in all countries outside the United States (even in jurisdictions where we and our licensors pursue patent protection) or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we and our licensors have not pursued and obtained patent protection to develop their own products, and they may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with our products and product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights

generally. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Issued patents covering our products and product candidates could be found invalid or unenforceable if challenged in court or in administrative proceedings. We may not be able to protect our trade secrets in court.

If we or one of our licensing partners initiate legal proceedings against a third party to enforce a patent covering one of our products or product candidates, should such a patent issue, the defendant could counterclaim that the patent covering our product or product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. An adverse determination in any of the foregoing proceedings could result in the revocation or cancellation of, or amendment to, our patents in such a way that they no longer cover our products or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant or third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our products and product candidates. Such a loss of patent protection could have a material adverse impact on our business.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach.

If we do not obtain patent term extension and data exclusivity for our products and product candidates, our business may be materially harmed.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our products and product candidates are obtained, once the patent life has expired for a product or product candidate, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products and product candidates similar or identical to ours.

In the future, if we obtain an issued patent covering one of our present or future product candidates, depending upon the timing, duration and specifics of any FDA marketing approval of such product candidates, such patent may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. A patent may only be extended once and only based on a single approved product. However, we may not be granted an extension because of, for example, failure to obtain a granted patent before approval of a product candidate, failure to exercise due diligence during the testing phase or regulatory review process, failure to apply within applicable

deadlines, failure to apply prior to expiration of relevant patents or otherwise our failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In addition, we do not control the efforts of our licensors to obtain a patent term extension, and there can be no assurance that they will pursue or obtain such extensions to patents that we may license from them.

Some intellectual property which we have in-licensed may have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements, and a preference for U.S. industry. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.

Some of the intellectual property rights we have licensed, 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.

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.

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, a court may decide not to grant an injunction against the offender and instead award only monetary damages, which may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our ADSs. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Any of the foregoing may have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Certain of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. Our licensors may face similar risks, which could have an adverse impact on intellectual property that is licensed to us.

We may be subject to claims challenging the inventorship or ownership of the patents and other intellectual property that we own or license.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own or such assignments may not be self-executing or may be breached. Our licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of

employees, consultants or others who are involved in developing our products or product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

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

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

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

Risks related to ownership of our securities

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

The trading price of our ADSs has fluctuated and is likely to continue to fluctuate significantly. The market price of our ADSs depends on a number of factors, some of which are beyond our control. In addition to the factors discussed in this "Item 1.A.—Risk Factors" and elsewhere in this Quarterly 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 adequately scale our manufacturing capabilities and commercial and sales organization to succeed in our commercialization efforts of Libmeldy and to achieve our expected timeline of commencing sales of Libmeldy;
- failure by us to succeed in our ongoing commercialization of Strimvelis;
- failure by us to gain broad insurance coverage and reimbursement for our product candidates, if approved;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial or other projections we may provide to the public;
- failure by us to meet or exceed the financial or other projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- general economic and market conditions, including the significant disruptions to the U.S. and global economies and the related significant volatility and negative pressure in financial markets caused by the COVID-19 global pandemic;
- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

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

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

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

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

Based upon our ordinary shares outstanding as of March 31, 2021, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 37.9% of our ordinary shares and ADSs. Depending on the level of attendance at our meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, 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.

Holders of ADSs are not treated as holders of our ordinary shares

Holders of our publicly traded securities are holders of ADSs with underlying ordinary shares in a company incorporated under English law. Holders of ADSs are not treated as holders of our ordinary shares, unless they withdraw the ordinary shares underlying their ADSs in accordance with the deposit agreement and applicable laws and regulations. The depositary is the holder of the ordinary shares underlying the ADSs. Holders of ADSs therefore do not have any rights as holders of our ordinary shares, other than the rights that they have pursuant to the deposit agreement.

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

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

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

We are entitled to amend the deposit agreement and to change the rights of the ADS holders under the terms of such agreement, without the prior consent of the ADS holders. We and the depositary may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us or to the depositary. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depositary. 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 depositary to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our ordinary shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility will terminate, ADS holders will receive at least 30 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but they will have no right to any compensation whatsoever.

ADSs holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that, to the fullest extent permitted by law, holders and beneficial owners of ADSs irrevocably waive the right to a jury trial of any claim they may have against us or the depositary arising out of or relating to the ADSs or the deposit agreement.

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs.

If any holders or beneficial owners of ADSs bring a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, such holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and/or the depositary. If a lawsuit is brought against us and/or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

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

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

Except as described in our Annual Report and this Quarterly Report and in the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the depositary to vote the ordinary shares underlying their ADSs. Otherwise, holders of ADSs will not be able to exercise their right to vote unless they withdraw the ordinary shares underlying their ADSs to vote them in person or by proxy in accordance with applicable laws and regulations and our Articles of Association. Even so, ADS holders may not know about a meeting far enough in advance to withdraw those ordinary shares. If we ask for the instructions of holders of the ADSs, the depositary, upon timely notice from us, will notify ADS holders of the upcoming vote and arrange to deliver our voting materials to them. Upon our request, the depositary will mail to holders a shareholder meeting notice that contains, among other things, a statement as to the manner in which voting instructions may be given. We cannot guarantee that ADS holders will receive the voting materials in time to ensure that they can instruct the depositary to vote the ordinary shares underlying their ADSs. A shareholder is only entitled to participate in, and vote at, the meeting of shareholders, provided that it holds our ordinary shares as of the record date set for such meeting and otherwise complies with our Articles of Association. In addition, the depositary's liability to ADS holders for failing to execute voting instructions or for the manner of executing voting instructions is limited by the deposit agreement. As a result, holders of ADSs may not be able to exercise their right to give voting instructions or to vote in person or by proxy and they may not have any recourse against the depositary or us if their ordinary shares are not voted as they have requested or if their shares cannot be voted.

Holders of our ADSs may not receive distributions on our ordinary shares represented by the ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

The depositary for the ADSs has agreed to pay to the holders of our ADSs the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses. Holders of our ADSs will receive these distributions in proportion to the number of our ordinary shares such holder's ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders of ADSs. We have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that holders of our ADSs may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available. These restrictions may have an adverse effect on the value of our ADSs.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be the sole source of gains to the holders of our ADSs and such holders may never receive a return on their investment.

Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be declared and paid. Therefore, we must have distributable profits before declaring and paying a dividend. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. As a result, capital appreciation, if any, on our ADSs will be the sole source of gains to the holders of our ADSs for the foreseeable future, and such holders may suffer a loss on their investment if they are unable to sell their ADSs at or above the price at which such holders purchased the ADSs.

Sales of a substantial number of our ADSs in the public market by our existing shareholders could cause the market price of our ADSs to drop significantly.

Sales of a substantial number of our ADS in the public market, or the perception that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. As of May 4, 2021, we had outstanding 123,769,373 voting and non-voting ordinary shares. The holders of 20,654,332 shares of our ordinary shares are entitled to rights with respect to the registration of their ordinary shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these ordinary shares under the Securities Act would result in the ADSs representing them becoming freely tradable without restriction, except for ADSs purchased by affiliates. In addition, our directors, executive officers and other affiliates may establish, and certain executive officers, directors and affiliates have established, programmatic selling plans under Rule 10b5-1 of the Exchange Act, for the purpose of effecting sales of our ADSs. Generally, sales under such plans by our executive officers and directors require public filings. Any sales of securities by these shareholders, or the perception that those sales may occur, under such programmed selling plans, could have a material adverse effect on the trading price of our ADSs. In addition, as of March 31, 2021, 16,389,965 ordinary shares reserved for issuance upon the

exercise of existing options outstanding and issuance of performance-based and time-based restricted shares under our current equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

We will continue to incur increased costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management is required to devote substantial time to new compliance initiatives.

As a public company listed on a U.S. Exchange, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel are required to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act ("Section 404"), we are required to furnish a report by our management on our internal control over financial reporting and, once we are no longer a "smaller reporting company", we will be required to furnish an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In order to achieve and maintain compliance with Section 404, we have documented and evaluated our internal control over financial reporting, which is both costly and challenging. In this regard, we continue to dedicate internal resources, have engaged outside consultants and adopted a detailed work plan to continually assess and document the adequacy of internal control over financial reporting, taken steps to improve control processes as appropriate, validated through testing that controls are functioning as documented and have implemented a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk in any given year that we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. Moreover, if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our ADSs could be negatively affected, and we could become subject to investigations by the SEC or other regulatory authorities or to shareholder litigation, which could have an adverse impact on the market price or our ADSs and cause us to incur additional expenses.

Shareholder protections and restrictions found in provisions under The City Code on Takeovers and Mergers do not apply to us.

In February 2020, the UK Takeover Panel confirmed that we are not considered to be subject to The City Code on Takeovers and Mergers, or The Takeover Code, and, as a result, our shareholders are not entitled to the benefit of certain takeover offer protections provided under The Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted and which may operate to prohibit certain arrangements and courses of conduct considered customary in the United States. There are no provisions in our Articles of Association that replicate the provisions of The Takeover Code.

We believe that this position is unlikely to change at any time in the near future, but in accordance with good practice, we will review the situation on a regular basis and cooperate and consult with the UK Takeover Panel if there is any material change in our circumstances with respect to matters which the UK Takeover Panel might consider relevant in their determination of jurisdiction over us.

The rights of our shareholders may differ from the rights typically offered to shareholders of a U.S. corporation.

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the UK Companies Act 2006, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations.

The principal differences include the following:

- Under English law and our Articles of Association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings.
- Under English law, it is only on a poll that the number of shares determines the number of votes a holder may cast. The voting rights of ADSs are also governed by the provisions of a deposit agreement with our depositary bank.
- Under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise.
- Under English law and our Articles of Association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the Articles of Association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve 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.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ADSs.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, testing required to be conducted by us in connection with Section 404, and subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

We are required to disclose changes made in our internal controls and procedures on a quarterly basis, and our management is required to assess the effectiveness of these controls annually. However, for as long as we are a “smaller reporting company,” our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404. We will qualify as a “smaller reporting company” if the market value of our ADSs held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of the last business day of our most recently completed second fiscal quarter. An independent assessment of the effectiveness of our internal control over financial reporting could detect problems that our management’s assessment might not. Undetected material weaknesses in our internal control over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well

conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Risks related to taxation

Changes in tax law could adversely affect our business and financial condition.

We conduct business globally. The tax treatment of the company or any of the group companies could be materially adversely affected by several factors, including, but not limited to: (i) changing tax laws, regulations and treaties, or the interpretation thereof; (ii) tax policy initiatives and reforms under consideration (such as those related to the Organization for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission's state aid investigations and other initiatives); (iii) the practices of tax authorities in jurisdictions in which we operate; and (iv) the resolution of issues arising from tax audits or examinations and any related interest or penalties. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid.

We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices in jurisdictions in which we operate, could affect our financial position, future results of operations, cash flows in a particular period and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders and increase the complexity, burden and cost of tax compliance.

Taxing authorities could challenge our historical and future tax positions or our allocation of taxable income among our subsidiaries, and tax laws to which we are subject could change in a manner adverse to us.

We operate through various subsidiaries in a number of countries throughout the world. Consequently, we are subject to tax laws, treaties, and regulations in the countries in which we operate, and these laws and treaties are subject to interpretation. We have taken, and will continue to take, tax positions based on our interpretation of such tax laws.

Our transfer pricing arrangements are not generally binding on applicable tax authorities. The price charged for products, services, or the royalty rates and other amounts paid for intellectual property rights, could be challenged by the various tax authorities, resulting in additional tax liability, interest, and/or penalties. There can be no assurance that a taxing authority will not have a different interpretation of applicable law and assess us with additional taxes. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a ''permanent establishment'' under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. If we are assessed with additional taxes, this may result in a material adverse effect on our results of operations and/or financial condition.

A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, for example where there has been a technical violation of contradictory laws and regulations that are relatively new and have not been subject to extensive review or interpretation, in which case we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable, or result in other liabilities.

If we are a controlled foreign corporation, there could be adverse U.S. federal income tax consequences to certain U.S. holders.

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to include in income for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of the CFC's "Subpart F income" and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. Subpart F income generally includes dividends, interest, rents, royalties, global intangible low-taxed income, gains from the sale of securities and income from certain transactions with related parties. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in a CFC may be required to classify a portion of such gain as dividend income rather than capital gain. A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the Code) who owns or is considered to own 10% or more of the total combined voting power of all classes of stock entitled to vote of such corporation. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain.

We believe that we were not a CFC in the 2020 taxable year, but we may become a CFC in a subsequent taxable year. If we are classified as both a CFC and a passive foreign investment company, or PFIC (as discussed below), we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

If we are a PFIC there could be adverse U.S. federal income tax consequences to U.S. holders.

Under the Code, we will be a PFIC, for any taxable year in which (i) 75% or more of our gross income consists of passive income or (ii) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. holder holds our 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 2020 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 UK net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable UK tax legislation.

As a UK incorporated and tax resident entity, we are subject to UK corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any UK corporation tax. As of December 31, 2020, we had cumulative carryforward tax losses of $390.1 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating

profits. The use of loss carryforwards in relation to UK profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of UK taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a company that carries out extensive research and development activities, we seek to benefit from two UK research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these tax credit cash rebate claims. Our eligibility to claim payable research and development tax credits may be limited or eliminated because we may no longer qualify as a small or medium-sized company. We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the UK research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

Our ability to use our U.S. tax attributes may be limited.

Under Section 382 and 383 of the Internal Revenue Code of 1986, as amended (the "Code"), 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 Section 382 of the Code. We may also experience ownership changes in the future as a result of subsequent shifts in our share ownership. As a result, if we incur U.S. federal tax liability, our ability to use our pre-change tax attributes carryforwards to offset U.S. federal tax liability may be subject to limitations, which could potentially result in increased future tax liability to us.

Risks related to our Domicile

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

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, or the Transition Period, started on the Exit Day and expired on December 31, 2020. During the Transition Period, most laws of the European Union continued to apply to the United Kingdom while the future relationship between the United Kingdom and the European Union was formally negotiated. The United Kingdom and the European Union have signed a EU-UK Trade and Cooperation Agreement, which became provisionally applicable on January 1, 2021 and will become formally applicable once ratified by both the United Kingdom and the European Union. This agreement provides details on how some aspects of the UK and EU's relationship will operate going forwards however there are still many uncertainties.

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 UK financial and banking markets, as well as on the regulatory process in Europe. As a result of Brexit, the EMA, formerly situated in London, relocated to Amsterdam. Further, there is considerable uncertainty resulting from a lack of precedent and the complexity of the United Kingdom and EU's intertwined legal regimes as to how Brexit, now that the Transition Period has expired, will impact the life sciences industry in Europe, including our company, including with respect to ongoing or future clinical trials. Since a significant proportion of the regulatory framework in the United Kingdom

applicable to our business and our product candidates is derived from EU directives and regulations, the withdrawal could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. The impact will largely depend on the model and means by which the United Kingdom's relationship with the European Union is governed post-Brexit. For example, now that the Transition Period has expired, Great Britain will no longer be covered by the centralized procedures for obtaining EEA-wide marketing authorization from the EMA, and a separate process for authorization of drug products, including our product candidates, will be required in Great Britain resulting in an authorization covering the United Kingdom or Great Britain only. For a period of two years from January 1, 2021, the MHRA may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a UK marketing authorization. A separate application will, however, still be required. The MHRA has published a series of guidance notes on how the process for authorization of medicines will now work, however exactly what implications this will have in practice remain unclear. As a result, we cannot predict the extent of the impact that Brexit will have on (i) the marketing of pharmaceutical products, (ii) the process to obtain regulatory approval in the United Kingdom for product candidates or (iii) the award of exclusivities that are normally part of the EU legal framework (for instance Supplementary Protection Certificates, Pediatric Extensions or Orphan exclusivity). 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 or the European Union and restrict our ability to generate revenue and achieve and sustain profitability.

Brexit may also result in a reduction of funding to the EMA if the United Kingdom no longer makes financial contributions to European institutions, such as the EMA. If UK funding is so reduced, it could create delays in the EMA issuing regulatory approvals for our product candidates and, accordingly, have a material adverse effect on our business, financial condition, results of operations or prospects.

In addition, we may be required to pay taxes or duties or be subjected to other hurdles in connection with the importation of our product candidates into the European Union, or we may incur expenses in establishing a manufacturing facility in the European Union in order to circumvent such hurdles. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom or the European Union for our product candidates, or incur significant additional expenses to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business.

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 UK laws and regulations as the United Kingdom determines which European Union rules and regulations to replicate or replace with its own rules and regulations (which may result in significant divergence from European rules and regulations), 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 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 how the EU-UK Trade and Cooperation Agreement, and any future agreements signed by the UK and the European Union, take effect in practice.

Such a withdrawal from the European Union is unprecedented, and it is unclear how the restrictions on 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.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. The United Kingdom will 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. 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.

Legal, political and economic uncertainty surrounding the United Kingdom's withdrawal from the European Union may be a source of instability in international markets, create significant currency fluctuations and risks of additional taxation, adversely affect our operations in the United Kingdom and pose additional risks to our business, revenue, financial condition, and results of operations.

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from European Union directives and regulations, Brexit, now that the Transition Period has expired, could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. For example, as a result of the uncertainty surrounding Brexit, the EMA relocated to Amsterdam from London. Following the expiry of the Transition Period, Great Britain will no longer be covered by the centralized procedures for obtaining EEA-wide marketing and manufacturing authorizations from the EMA (under the Northern Irish Protocol, centralized marketing authorizations will continue to be recognized in Northern Ireland) and a separate process for authorization of drug products will be required in Great Britain resulting in an authorization covering Great Britain only. 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 or the European Union and limit 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 or the European Union for our product candidates, or incur significant additional expenses to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the United Kingdom. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the European Union.

The uncertainty concerning the United Kingdom's legal, political and economic relationship with the European Union following 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). It is possible, now that the Transition Period has expired, that the application of charges to stamp duty and stamp duty reserve tax to issues or transfers of our ordinary shares to depositary receipt systems or clearance services could be affected. Although under current law and Her Majesty's Revenue & Customs published practice it is not expected that any stamp duty or stamp duty reserve tax, or SDRT, would arise in respect of any issue or transfer of our ordinary shares into a clearance service or depositary receipt system where it forms an integral part of capital raising, it is possible, now that the Transition Period has expired, that existing legislation (which was not previously enforceable but which the Government indicated in April 2017 and HMRC confirmed in their January 2021 Newsletter would not be applied following Brexit) could be applied, for example in the event of a change in Government policy, such that stamp duty and/or SDRT would apply in respect of any issue or transfer of our ordinary shares occurring thereafter including in respect of an issue or transfer which is integral to the raising of capital. In this event, we may be expected to bear any such stamp duty or SDRT (which, based on the existing legislation would be charged, in effect, at the rate of 1.5% of the value of the ordinary shares so issued or transferred). Any such charge would therefore represent an additional cost of our seeking to raise additional capital through further issuances of our ordinary shares.

Exchange rate fluctuations may materially affect our results of operations and financial condition.

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. These adverse impacts may be exacerbated by the ongoing economic dislocation caused by the COVID-19 global pandemic. Although we are based in the United Kingdom, we source research and development, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

Claims of U.S. civil liabilities may not be enforceable against us.

We are incorporated under English law. Certain members of our board of directors and senior management are non-residents of the United States, and a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether UK courts would entertain original actions brought in the United Kingdom against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of the United Kingdom as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that certain requirements are met. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement.

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

General Risk Factors

We have debt service obligations and may incur additional indebtedness in the future, which could adversely affect our financial condition 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, as amended April 7, 2020, 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, share capital, enter into transactions with affiliates or materially change our business.

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. 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.

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 UK Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA will no longer persuade or compel banks to submit rates for the calculation of LIBOR after 2021. 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.

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.

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.

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 qualified 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 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, the regulatory and compliance costs to us under U.S. securities laws have been higher than the costs we incurred as a foreign private issuer, and therefore, the loss of foreign private issuer status has increased our legal and financial compliance costs. We 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 may 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, or 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, 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.

Even though we no longer qualify as an emerging growth company, we will qualify as a "smaller reporting company" if the market value of our ADSs held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of the last business day of our most recently completed second fiscal quarter, which would allow us to take advantage of many of the same exemptions from disclosure requirements.

Item 2. Unregistered Sales of Equity Securities and Use of Proceeds.

Sales of Unregistered Securities

During the quarter ended March 31, 2021, we did not have any sales of unregistered securities except as detailed on the Company's Current Report on Form 8-K, filed February 9, 2021.

Item 3. Defaults Upon Senior Securities.

Not applicable.

Item 4. Mine Safety Disclosures.

Not applicable.

Item 5. Other Information.

Not applicable.

Item 6. Exhibits.

Exhibit Number	Description
10.1	Securities Purchase Agreement dated February 4, 2021, by and among Orchard Therapeutics plc and the Purchasers named therein (as filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on February 9, 2021 and incorporated herein by reference).
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 Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

* Indicates the exhibit is being furnished, not filed, with this report

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

ORCHARD THERAPEUTICS PLC

Date: May 13, 2021

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: May 13, 2021

By: /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer
(Principal Financial Officer and Principal Accounting Officer)

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Bobby Gaspar, certify that:

1. I have reviewed this quarterly report of Orchard Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 13, 2021

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

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Frank E. Thomas, certify that:

1. I have reviewed this quarterly report of Orchard Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: May 13, 2021

By: /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report of Orchard Therapeutics plc(the "Company") on Form 10-Q for the period ending March 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers does hereby certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: May 13, 2021

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: May 13, 2021

By: /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer
(Principal Financial Officer and Principal Accounting Officer)