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, 2023

OR

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

For the transition period from to

Commission File Number: 001-38722

ORCHARD THERAPEUTICS PLC

(Exact Name of Registrant as Specified in its Charter)

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

245 Hammersmith Road
London W6 8PW
United Kingdon

(Address of principal executive offices)

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

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

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

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

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 ☒

As of May 9, 2023, the Registrant had 184,260,149 ordinary voting and non-voting shares, nominal value £0.10 per share, outstanding, which if all held in ADS form would be represented by 18,426,014 American Depositary Shares, each representing ten ordinary shares.

Summary of the Material Risks Associated with Our Business

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

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

The summary risk factors described above should be read together with the text of the full risk factors below, in the section entitled "*Risk Factors*" in Part II, Item 1.A. and the other information set forth in this Quarterly Report on Form 10-Q, 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 pre-clinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work and the period during which the results of the trials or studies will become available;
- the timing, scope and likelihood of regulatory submissions, filings and approvals, including our expectations and timing to complete our biologics license application, or BLA, for OTL-200, currently expected in mid-2023;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the market opportunity for and size of the patient populations for Libmeldy (OTL-200) and our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial products, product candidates and technology;
- our plans and ability to build out our commercial infrastructure and successfully identify eligible patients for Libmeldy in Europe and our product candidates, if approved for commercial use;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of Libmeldy and any of our product candidates, if approved, including reimbursement for patients treated in a country where they are not a resident;
- the adequacy, scalability and commercial viability of our manufacturing capacity, methods and processes, including those of our manufacturing partners, and our plans for future development;
- the rate and degree of market acceptance and clinical utility of our commercial products and product candidates and gene therapy in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- the impact of the COVID-19 global pandemic on our business operations;
- our competitive position;
- the scope of protection we and our licensors are able to establish and maintain for intellectual property rights covering our commercial products and product candidates;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our ability to attract and retain qualified employees and key personnel;
- our ability to contract with third-party suppliers, clinical sites and manufacturers and their ability to perform adequately;
- our projected financial condition, including the sufficiency of our cash, cash equivalents and investments to fund operations in future periods and future liquidity, working capital and capital requirements; and
- other risks and uncertainties, including those listed under the caption “Item 1A. Risk Factors” 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 share and per share amounts)
(unaudited)

	March 31, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 61,487	$ 68,424
Marketable securities	84,828	75,326
Accounts receivable	—	8,467
Prepaid expenses and other current assets	13,810	9,986
Research and development tax credit receivable	6,075	5,942
Total current assets	166,200	168,145
Non-current assets:		
Operating lease right-of-use-assets	21,904	22,774
Property and equipment, net	8,149	8,138
Research and development tax credit receivable	769	—
Restricted cash	4,215	4,215
Intangible assets, net	3,518	3,560
Other assets	12,262	12,075
Total non-current assets	50,817	50,762
Total assets	$ 217,017	$ 218,907
Liabilities and Shareholders' Equity		
Current liabilities:		
Accounts payable	$ 8,772	$ 9,318
Accrued expenses and other current liabilities	27,984	34,437
Deferred revenue, current	634	959
Operating lease liabilities	6,467	6,424
Notes payable, current	9,429	9,429
Total current liabilities	53,286	60,567
Notes payable, long-term	20,717	22,991
Deferred revenue, net of current portion	10,779	10,315
Operating lease liabilities, net of current portion	16,657	19,246
PIPE Warrant and PIPE Unit liabilities	6,186	—
Other long-term liabilities	7,737	7,524
Total liabilities	115,362	120,643
Commitments and contingencies (see Note 15)		
Shareholders' equity:		
Ordinary shares (voting and non-voting), £0.10 par value; Most recent authority to allot up to a maximum nominal value of £13,023,851.50 of shares at March 31, 2023 and December 31, 2022, respectively; Issued and outstanding — 184,256,359 and 126,947,225 shares at March 31, 2022 and December 31, 2022, respectively.	23,871	16,419
Additional paid-in capital	975,719	956,711
Accumulated other comprehensive income	20,361	26,018
Accumulated deficit	(918,296)	(900,884)
Total shareholders' equity	101,655	98,264
Total liabilities and shareholders' equity	$ 217,017	$ 218,907

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,	
	2023	**2022**
Product revenue, net	$ 534	$ 5,059
Collaboration revenue	703	465
Total revenue	1,237	5,524
Costs and operating expenses:		
Cost of product revenue	367	1,571
Research and development	15,993	28,234
Selling, general and administrative	11,135	13,299
Total costs and operating expenses	27,495	43,104
Loss from operations	(26,258)	(37,580)
Other income (expense):		
Interest income	1,029	69
Interest expense	(957)	(675)
Changes in fair value of PIPE Warrant and PIPE Unit liabilities	3,852	—
Other income (expense), net	4,910	(6,052)
Total other income (expense), net	8,834	(6,658)
Net Loss before income taxes	(17,424)	(44,238)
Income tax benefit (expense)	12	(58)
Net loss attributable to ordinary shareholders	$ (17,412)	$ (44,296)
Net loss per ordinary share attributable to ordinary shareholders, basic and diluted	$ (0.12)	$ (0.35)
Weighted average ordinary shares outstanding, basic and diluted	141,809,004	127,694,785
Other comprehensive income:		
Foreign currency translation adjustment	(5,731)	5,595
Unrealized gain (loss) on marketable securities	74	(260)
Total other comprehensive income (loss)	(5,657)	5,335
Total comprehensive loss	$ (23,069)	$ (38,961)

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements of Shareholders' Equity

(In thousands, except share and per share amounts)

(unaudited)

	Ordinary Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total
	Shares	Amount				
Balance at December 31, 2021	**125,674,095**	**$ 16,253**	**$ 940,675**	**$ 3,246**	**$ (750,224)**	**$ 209,950**
Share-based compensation expense	—	—	4,660	—	—	4,660
Exercise of share options	222,381	28	(29)	—	—	(1)
Vesting of restricted stock units, net of shares withheld for taxes	3,217	1	(4)	—	—	(3)
Ordinary shares issued as part of a consulting agreement	5,252	1	—	—	—	1
Foreign currency translation	—	—	—	5,595	—	5,595
Unrealized loss on available for sale debt securities	—	—	—	(260)	—	(260)
Net loss attributable to ordinary shareholders	—	—	—	—	(44,296)	(44,296)
Balance at March 31, 2022	**125,904,945**	**$ 16,283**	**$ 945,302**	**$ 8,581**	**$ (794,520)**	**$ 175,646**
Balance at December 31, 2022	**126,947,225**	**$ 16,419**	**$ 956,711**	**$ 26,018**	**$ (900,884)**	**$ 98,264**
Share-based compensation expense	—	—	3,512	—	—	3,512
Exercise of share options	332,209	43	(2)	—	—	41
Vesting of restricted stock units, net of shares withheld for taxes	310,025	40	(206)	—	—	(166)
Sale of voting and non-voting ordinary shares, net of issuance costs of $889	56,666,900	7,369	15,704	—	—	23,073
Foreign currency translation	—	—	—	(5,731)	—	(5,731)
Unrealized loss on available for sale debt securities	—	—	—	74	—	74
Net loss attributable to ordinary shareholders	—	—	—	—	(17,412)	(17,412)
Balance at March 31, 2023	**184,256,359**	**$ 23,871**	**$ 975,719**	**$ 20,361**	**$ (918,296)**	**$ 101,655**

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements of Cash Flows

(In thousands, except share and per share amounts)

(unaudited)

	Three Months Ended March 31,	
	2023	2022
Cash flows from operating activities:		
Net loss attributable to ordinary shareholders	$ (17,412)	$ (44,296)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	643	709
Share-based compensation	3,512	4,660
Non-cash interest expense	121	94
Amortization of provision on loss contract	—	(274)
Amortization of premium on marketable securities	(592)	187
Deferred income taxes	242	787
Change in fair value of warrant and tranche obligation liabilities	(3,852)	—
Unrealized foreign currency and other non-cash adjustments	(6,197)	5,984
Changes in operating assets and liabilities:		
Accounts receivable	8,599	(2,719)
Research and development tax credit receivable	(769)	13,483
Prepaid expenses, other current assets and other assets	(4,136)	(62)
Operating leases, right-of-use assets	1,114	1,455
Accounts payable, accrued expenses and other liabilities	(7,912)	3,815
Deferred revenue	(107)	(65)
Operating lease liabilities	(2,762)	(3,357)
Net cash used in operating activities	(29,508)	(19,599)
Cash flows from investing activities:		
Proceeds from sales and maturities of marketable securities	30,000	55,186
Purchases of marketable securities	(38,832)	(29,681)
Purchases of property and equipment	(514)	(398)
Net cash provided by (used in) investing activities	(9,346)	25,107
Cash flows from financing activities:		
Proceeds from employee equity plans	41	—
Payment of taxes on restricted stock vesting	(166)	—
Proceeds from the issuance of shares in private placement	34,000	—
Payment of placement agent fees and offering costs in connection with private placement	(12)	—
Repayment of notes payable	(2,357)	—
Net cash provided by financing activities	31,506	—
Effect of exchange rate changes on cash, cash equivalents, and restricted cash	411	(645)
Net increase in cash, cash equivalents and restricted cash	(6,937)	4,863
Cash, cash equivalents, and restricted cash, beginning of period	72,639	60,178
Cash, cash equivalents, and restricted cash, end of period	$ 65,702	$ 65,041
Supplemental disclosure of non-cash activities:		
Private placement offering costs in accounts payable and accrued expenses	$ 1,606	$ —
Intangible assets and property and equipment in accounts payable and accrued expenses	$ 104	$ 1,102
Supplemental disclosure of cash flow information:		
Lease assets obtained in exchange for new operating lease liabilities	$ —	$ 4,912
Cash paid for interest	$ 812	$ 581

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

1. Nature of the Business and Liquidity

Orchard Therapeutics plc (the "Company") is a global gene therapy company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. The Company's *ex vivo* autologous hematopoietic stem cell ("HSC") gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Company has a portfolio that includes a commercial-stage product and research and development-stage product candidates.

The Company is a public limited company incorporated pursuant to the laws of England and Wales. The Company has American Depositary Shares ("ADSs") registered with the U.S. Securities and Exchange Commission (the "SEC"). The ADSs were listed on the Nasdaq Global Select Market on October 31, 2018, and were transferred to the Nasdaq Capital Market on September 13, 2022. The Company's ADSs each represent ten ordinary shares of the Company. Each holder of ordinary shares is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. The Company did not declare any dividends in 2023 or 2022. Share information presented in these condensed consolidated financial statements are presented on an ordinary share basis and not on an ADS converted basis unless otherwise indicated.

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

On March 6, 2023, the Company entered into a Securities Purchase Agreement pursuant to which the Company agreed to sell ordinary shares, non-voting ordinary shares, and warrants to purchase ordinary shares or non-voting ordinary shares in an unregistered offering (the "2023 Private Placement"). The 2023 Private Placement consists of two closings. On March 10, 2023, the Company completed the initial closing and issued and sold (i) 56,666,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share and (ii) warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The initial closing of the 2023 Private Placement resulted in gross proceeds of $34.0 million. Refer to Footnote 10 for further discussion around the 2023 Private Placement.

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

Through March 31, 2023, the Company funded its operations primarily with proceeds from the sale of equity securities, including ADSs in the Company's initial public offering ("IPO") and follow-on offering, ordinary shares in the private placements, and convertible preferred shares. The Company has also financed its operations through proceeds from the Company's senior term facilities agreement with MidCap Financial (Ireland) Limited, research grants from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from the Company's collaboration agreement and share purchase agreement with Pharming Group N.V., proceeds from the sales of the Company's Libmeldy product, and reimbursements associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program. The Company has incurred recurring losses since its inception and expects to continue to generate operating losses for the foreseeable future.

The Company expects that its cash, cash equivalents, and marketable securities on hand as of March 31, 2023, of $146.3 million, together with expected proceeds from sales of Libmeldy, will be sufficient to fund its operations, capital expenditures and debt service payments for at least twelve months from the date of filing of this Form 10-Q. 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. 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 U.S. generally accepted accounting principles ("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 GAAP for complete financial statements. Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in the Accounting Standards Codification ("ASC"), and Accounting Standards Update ("ASU"), of the Financial Accounting Standards Board ("FASB").

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 14, 2023 (the "Annual Report"). The condensed consolidated balance sheet as of December 31, 2022, was derived from audited consolidated financial statements included in the Company's Annual Report but does not include all disclosures required by GAAP.

Certain information and footnote disclosures normally included in financial statements prepared in accordance with 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 in thousands, except percentages, per share amounts or as otherwise noted. As a result, certain totals may not sum due to rounding.

Principles of consolidation

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

Segment information

The Company operates in a single segment focusing on researching, developing and commercializing potentially curative gene therapies. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, the results of the Company's operations are reported on a consolidated basis for the purposes of segment reporting.

Use of estimates

The preparation of condensed consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the 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, collaboration agreement milestones, variable consideration in revenue recognition, operating lease assets and liabilities, valuation of PIPE Warrants and PIPE Units, 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. Unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar, Pounds sterling, and Euro exchange rates. Translation gains and losses are included in accumulated other comprehensive income (loss) in shareholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations. The Company recorded realized and unrealized foreign currency transaction losses of $5.6

million for the three months ended March 31, 2023, and realized and unrealized foreign currency transaction losses of $6.1 million for the three months ended March 31, 2022, which is included in other income (expense), net in the condensed consolidated statements of operations and comprehensive loss.

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 securities

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

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

Accounts receivable

Accounts receivable arise from product revenue and amounts due from the Company's collaboration partners and have payment terms that generally require payment within 30 to 90 days. For some Libmeldy customers, our payment terms can range from 30 days to under one year. The amount from product revenue represents amounts due from distributors in Europe, which are recorded net of reserves for trade discounts and allowances, and other incentives to the extent such amounts are payable to the customer by the Company. The Company monitors economic conditions to identify facts or circumstances that may indicate that its receivables are at risk of collection. The Company provides reserves against accounts receivable for estimated losses, if any, that may result from a customer's inability to pay based on the composition of its accounts receivable, current economic conditions, and historical credit loss activity. Amounts determined to be uncollectible are charged or written-off against the reserve. During the three months ended March 31, 2023, the Company did not record any expected credit losses related to outstanding accounts receivable.

Fair Value Measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

Level 1—Valuations based on quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly, such as quoted market prices, interest rates, and yield curves.

Level 3—Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable.

To the extent a valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair values requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

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

Restricted cash

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 sheets. The Company has an outstanding letter of credit for $3.0 million associated with a lease and is required to hold this amount in a standalone bank account, as of March 31, 2023, and December 31, 2022. 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, 2023 and December 31, 2022.

The Company includes the restricted cash balance in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown in 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 sheets that sum to the total of the amounts reported in the unaudited condensed consolidated statement of cash flows (in thousands):

	As of March 31, 2023	As of December 31, 2022
Cash and cash equivalents	$ 61,487	$ 68,424
Restricted cash	4,215	4,215
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 65,702	$ 72,639

United Kingdom research and development tax credit

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

The RDEC and SME credits are not dependent on the Company generating future taxable income or on the ongoing tax status or tax position of the Company. Each reporting period, the Company assesses its research and development activities and expenditures to determine whether the nature of these costs will qualify for credit under the tax relief programs and whether the claims will ultimately be realized based on the allowable reimbursable expense criteria established by the UK government. The Company expects a proportion of expenditures incurred in relation to its pipeline research, clinical trials management, and manufacturing development activities to be eligible for the research and development tax relief programs for the year ended December 31, 2023. The Company has qualified under the more favorable SME regime for the year ended December 31, 2022, and expects to qualify under the SME regime for the year ending December 31, 2023.

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 periods (amounts in thousands):

	Three Months Ended	
	2023	2022
Balance at beginning of period	$ 5,942	$ 30,723
Recognition of credit claims as offset to research and development expense	769	3,337
Receipt of credit claims	—	(16,474)
Foreign currency translation	133	(937)
Balance at end of period	$ 6,844	$ 16,649

As of March 31, 2023, $6.1 million of the Company's tax incentive receivable from the UK government was classified as current. As of March 31, 2022, $13.4 million of the Company's tax incentive receivable from the UK government was classified as current.

Product revenue, net

Libmeldy

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

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

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

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

Amounts are recorded as accounts receivable when the right to the consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. The Company expenses incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that would have been recognized is one year or less or the amount is immaterial. As of March 31, 2023, the Company has not capitalized any costs to obtain contracts.

The Company recognizes product revenue, net of variable consideration related to certain allowances and accruals, when the customer takes control of the product, which is at a point in time once the patient has been infused. Product revenue is recorded at the net sales price, or transaction price. The Company records estimated product revenue reserves, which are classified as a reduction in product revenue, to account for the components of variable consideration. Variable consideration includes the following components: government rebates, including performance-based rebates, trade discounts and allowances, and other incentives, which are described below.

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

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

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

Product returns: Based on the timing of revenue recognition upon treatment with the patient, the Company does not expect any returns of the Company’s products.

Other incentives: While the Company does not currently have any other incentives that have been recorded to date, the Company may enter into future arrangements that have other incentives that will be recorded as a reduction of revenue.

Strimvelis

The Company's product sales of Strimvelis are currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. The hospital will purchase and pay for the products and submit a claim to the payer. The Company's contracted sales with the hospital contains a single performance obligation and the Company recognizes revenue from product sales when the Company has satisfied its performance obligation, which is upon transferring control of the products to the hospital. The Company evaluated the variable consideration under ASC 606 and there is currently no variable consideration included in the transaction price for the products. Costs to manufacture and deliver the product and those associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates there is limited risk of product return, including the risk of product expiration.

Net loss per ordinary share

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

	March 31,	
	2023	2022
Share options	16,477,119	13,113,339
Unvested restricted incentive shares	3,298,969	500,989
Ordinary shares to be issued upon exercise of warrants	62,333,590	—
	82,109,678	13,614,328

Recently adopted accounting pronouncements

In March 2020, the FASB issued ASU 2020-04, Reference Rate Reform (Topic 848)*: Facilitation of the Effects of Reference Rate Reform on Financial Reporting* and issued two subsequent amendments: ASU 2021-01, issued in January 2021, refines the scope of ASU and clarifies some of its guidance as part of the FASB's monitoring of global reference rate reform activities and ASU 2022-06, issued in December 2022, which extends the effective period of the ASU through December 31, 2023 (collectively, including ASU 2020-04, "ASC 848"). ASC 848 provides temporary optional expedients and exceptions to the GAAP guidance on contract modifications and hedge accounting to ease the financial reporting burdens related to the expected market transition from the London Interbank Offered Rate ("LIBOR") and other interbank offered rates to alternative reference rates. ASC 848 is effective for all entities as of March 12, 2020, through December 31, 2024, at which time transition is expected to be complete. The Company adopted and applied the amendments of this ASU to its disclosures as of March 31, 2023. The application of this ASU did not have a material impact on the Company's financial position, results of operations, or cash flows.

3. Fair value measurements and marketable securities

Fair value measurements

The following tables present information about the Company's financial assets and liabilities that have been measured at fair value as of March 31, 2023, and December 31, 2022, and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

	Fair Value Measurements as of March 31, 2023			
	Level 1	Level 2	Level 3	Total
Assets				
Cash equivalents				
Money market funds	$ 3,550	$ —	$ —	$ 3,550
U.S. treasuries	—	—	—	—
U.S. government securities	—	—	—	—
Commercial paper	—	30,151	—	30,151
Total cash equivalents	$ 3,550	$ 30,151	$ —	$ 33,701
Marketable securities				
U.S. government securities	$ —	$ 7,896	$ —	$ 7,896
Corporate bonds	—	16,598	—	16,598
Commercial paper	—	60,334	—	60,334
Total marketable securities	$ —	$ 84,828	$ —	$ 84,828
Total Assets	$ 3,550	$ 114,979	$ —	$ 118,529
Liabilities				
PIPE Warrant liability	$ —	$ —	$ 6,179	$ 6,179
PIPE Units liability	—	—	7	7
Total Liabilities	$ —	$ —	$ 6,186	$ 6,186

	Fair Value Measurements as of December 31, 2022			
	Level 1	Level 2	Level 3	Total
Assets				
Cash equivalents				
Money market funds	$ 1,239	$ —	$ —	$ 1,239
U.S. treasuries	—	6,600	—	6,600
U.S. government securities	—	5,200	—	5,200
Commercial paper	—	14,122	—	14,122
Total cash equivalents	$ 1,239	$ 25,922	$ —	$ 27,161
Marketable securities				
U.S. government securities	$ —	$ 1,984	$ —	$ 1,984
Corporate bonds	—	25,475	—	25,475
Commercial paper	—	47,867	—	47,867
Total marketable securities	$ —	$ 75,326	$ —	$ 75,326
Total Assets	$ 1,239	$ 101,248	$ —	$ 102,487

The Company classifies its money market funds as Level 1 assets since it measures fair value using quoted prices in active markets for identical assets. The Level 2 assets include commercial paper, U.S. government securities, U.S. treasuries, and corporate bonds and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data.

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

On March 6, 2023, in connection with the 2023 Private Placement, the Company entered into a Securities Purchase Agreement with several investors, pursuant to which the Company agreed to sell, in two separate closings, voting and non-voting ordinary shares, and warrants to purchase ordinary shares or non-voting ordinary shares. On March 10, 2023, the Company completed the initial closing of the 2023 Private Placement and issued the PIPE Warrants (as defined in Note 10) to purchase a total of 62,333,590 ordinary shares or non-voting ordinary shares. In the second closing of the 2023 Private Placement, the Company is contingently obligated to issue the PIPE Units (as defined in Note 10) upon the occurrence of certain events.

The PIPE Warrants and the PIPE Units did not meet the criteria for equity classification at issuance or as of March 31, 2023, and are therefore classified as non-current liabilities on the accompanying condensed consolidated balance sheets. Changes in the fair value of the PIPE Warrants and the PIPE Units are recognized as a component of other income (expense), net in the consolidated statement of operations and comprehensive loss.

The fair values of the PIPE Warrants and PIPE Units liabilities are based on significant unobservable inputs, which represent Level 3 measurements within the fair value hierarchy. The fair value of the PIPE Warrants was estimated using the Black-Scholes option

pricing model and then adjusted by a weighted probability of the timing of anticipated achievement of FDA marketing approval for the sale of Libmeldy in the United States and then further adjusted by the weighted probability of the occurrence of the achievement of FDA marketing approval for the sale of Libmeldy in the United States and successful completion of the Second Closing.

The fair value of the PIPE Units was estimated as the residual of the fair value of the share and warrant units to be sold in the Second Closing minus the second closing sales price of the share and warrant units to be sold. To calculate the fair value of the shares to be sold in the Second Closing, the Company utilized the stock price of its ADSs as of the valuation date and discounted it using a discount for lack of marketability (DLOM). The fair value of the warrants to be sold in the Second Closing was estimated using the Black-Scholes option pricing model and then adjusting by the probability of occurrence of achievement of FDA marketing approval for the sale of Libmeldy in the United States.

The significant unobservable inputs used in the valuation model to measure the PIPE Warrants and PIPE Units liabilities are as follows at the issuance date and as of March 31, 2023:

	PIPE Warrants		PIPE Units	
	March 10, 2023	March 31, 2023	March 10, 2023	March 31, 2023
Black-Scholes inputs	(Issuance date)		(Issuance date)	
Anticipated common stock price (at exercise date)	$10.00 - $10.31	$10.13 - $10.38	$10.14 - $10.46	$10.23 - $10.49
Expected term (in years)	1.39 - 2.14	1.33 - 2.08	1.08 - 1.84	1.08 - 1.84
Expected volatility	72.9% - 76.0%	71.7% - 77.4%	72.9% - 76.0%	71.7% - 77.4%
Other significant unobservable inputs				
Implied probabilities of occurrence of Second Closing and FDA Approval				47.0% - 59.0%
Discount for lack of marketability				11.9% - 12.5%

The following table provides a rollforward of the aggregate fair values of the Company's PIPE Warrant liability and PIPE Unit liability, for which fair values are determined using Level 3 inputs (in thousands):

	PIPE Warrant Liability	PIPE Unit Liability
Balance at December 31, 2022	$ —	$ —
Issuances during period	6,455	25
Change in fair value	(276)	(18)
Balance at March 31, 2023	$ 6,179	$ 7

Marketable securities

The following tables summarize the amortized cost and fair value of the Company's available-for-sale marketable debt securities (in thousands):

	March 31, 2023				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
U.S. government securities	$ 7,904	$ —	$ (8)	$ —	$ 7,896
Corporate bonds	16,711	2	(115)	—	16,598
Commercial paper	90,523	—	(38)	—	90,485
Total	$ 115,138	$ 2	$ (161)	$ —	$ 114,979

	December 31, 2022				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
U.S. government securities	$ 7,188	$ 1	$ (6)	$ —	$ 7,183
U.S. treasuries	6,599	1	—	—	$ 6,600
Corporate bonds	25,656	—	(180)	—	$ 25,476
Commercial paper	62,038	3	(52)	—	61,989
Total	$ 101,481	$ 5	$ (238)	$ —	$ 101,248

All investments in an unrealized loss position were in this position for less than 12 months. The Company evaluated its securities for potential other-than-temporary impairment and considered the decline in market value to be primarily attributable to current economic

and market conditions. Additionally, the Company does not intend to sell the securities in an unrealized loss position and does not expect it will be required to sell the securities before recovery of the unamortized cost basis. Given the Company's intent and ability to hold such securities until recovery, and the lack of a significant change in credit risk for these investments, the Company does not consider these investments to be impaired as of March 31, 2023.

There were no realized gains or losses recognized on investments in the three months ended March 31, 2023.

The following table summarizes the Company’s debt securities by contractual maturity, as of March 31, 2023, and December 31, 2022 (in thousands):

	March 31, 2023	December 31, 2022
Maturities in one year or less	$ 111,000	$ 98,277
Maturities between one and three years	3,979	2,971
Total	$ 114,979	$ 101,248

4. Prepaid expenses and other current assets

Prepaid expenses and other current assets consist of the following (in thousands):

	March 31, 2023	December 31, 2022
Prepaid external research and development expenses	$ 1,227	$ 881
Inventories	5,555	3,400
Other prepayments	3,999	1,817
VAT receivable	1,013	1,077
Non-trade receivables	1,020	1,851
Rent deposits	996	960
Total prepaid expenses and other current assets	$ 13,810	$ 9,986

5. Intangible assets, net

Intangible assets, net of accumulated amortization, consisted of the following (in thousands):

	As of March 31, 2023		
	Cost	Accumulated Amortization	Net
License milestones	$ 4,119	$ (601)	$ 3,518
Total	$ 4,119	$ (601)	$ 3,518

	As of December 31, 2022		
	Cost	Accumulated Amortization	Net
License milestones	$ 4,069	$ (509)	$ 3,560
Total	$ 4,069	$ (509)	$ 3,560

License intangibles consist of capitalized milestone payments or accruals of payments the Company has deemed probable upon receiving regulatory approval of Libmeldy in the EU. The license intangibles are being amortized on a straight-line basis over the remaining useful life of the related patents of approximately twelve years. Amortization of intangible assets totaled $0.1 million for the three months ended March 31, 2023 and 2022, respectively. The effect of foreign currency translation on the net carrying value of intangible assets for the three months ended March 31, 2023 and 2022, was $0.1 million, respectively. The following table summarizes the estimated future amortization for intangible assets for the next five years and thereafter (in thousands):

	As of March 31, 2022
2023 (remaining nine months)	$ 256
2024	342
2025	342
2026	342
2027	342
Thereafter	1,894
Total	$ 3,518

6. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	March 31, 2023	December 31, 2022
Accrued external research and development expenses	$ 9,993	$ 11,230
Accrued payroll and related expenses	6,823	12,312
Accrued professional fees	2,602	2,263
Accrued other	2,483	2,647
Accrued governmental rebates	2,349	2,300
Strimvelis liability - current portion	3,734	3,685
Total accrued expenses and other current liabilities	$ 27,984	$ 34,437

7. Notes payable

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

In May 2021, the Company amended and restated the Original Credit Facility (the “Amended Credit Facility”). Under the Amended Credit Facility, the Lenders agreed to make term loans available to the Company in the aggregate amount of $100.0 million, including increasing the principal on the initial term loan to $33.0 million, from $25.0 million. In January 2023, the Company again amended and restated the credit facility to change from LIBOR to SOFR. As of March 31, 2023, the Company has borrowed $33.0 million under the Amended Credit Facility

In March 2023, the Company notified MidCap Financial of its voluntary cancellation of each Lender's remaining commitments under the Amended Credit Facility. As a result of this notice, the Company forwent the ability to draw down on any of the remaining $67.0 million available on the Amended Credit Facility and MidCap agreed to waive certain restrictive covenants of the Amended Credit Facility, specifically related to restrictions on the Company's ability to dispose of intellectual property related to deprioritized products.

The Company's borrowings under the Amended Credit Facility bear interest at an annual rate equal to 5.95% plus SOFR plus a 0.10% annual increase to the annual rate. The Company was required to make interest only payments on the term loan for 18 months following the date of the Amended Credit Facility. The term loan under the Amended Credit Facility began amortizing on the 18-month anniversary of the Amended Credit Facility (December 2022), with the Company commencing equal monthly payments of principal plus interest to the Lenders to be made in consecutive monthly installments until the loan maturity date. In addition, a final payment of 3.5% is due on the loan maturity date. The Company is accruing the final payment amount of $1.2 million associated with the Amended Credit Facility, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the loan maturity date.

The Amended Credit Facility includes affirmative and negative covenants. The affirmative covenants include, among others, covenants requiring the Company to maintain their legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage, maintain property, pay taxes, satisfy certain requirements regarding accounts and comply with laws and regulations. The negative covenants include, among others, restrictions on the Company transferring collateral, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, making investments, creating liens, amending material agreements and organizational documents, selling assets, changing the nature of the business and undergoing a change in control, in some cases subject to certain exceptions.

Notes payable consist of the following (in thousands):

	March 31, 2023	December 31, 2022
Notes payable, net of issuance costs	$ 29,634	$ 31,970
Less: current portion	(9,429)	(9,429)
Notes payable, net of current portion	20,205	22,541
Accretion related to final payment	512	450
Notes payable, long term	$ 20,717	$ 22,991

As of March 31, 2023, the estimated future principal payments due are as follows (in thousands):

	Aggregate Minimum Payments
2023 (remaining nine months)	$ 7,071
2024	9,429
2025	9,429
2026	5,084
Total	31,013
Less current portion	(9,429)
Less unamortized portion of final payment	(642)
Less unamortized debt issuance costs	(225)
Notes payable, long term	$ 20,717

During the three months ended March 31, 2023 and 2022, the Company recognized $1.0 million and $0.7 million of interest expense related to the term loan, respectively. The effective annual interest rate as of March 31, 2023, was approximately 11.78%.

8. Shareholders' equity

The Company's ordinary shares are divided into two classes: (1) Ordinary Shares and (2) Non-Voting Ordinary Shares. The Non-Voting Ordinary Shares have the same rights and restrictions as the Ordinary Shares and shall otherwise rank *parri passu* in all respects with the Ordinary Shares and a holder of Ordinary Shares shall be subject to the same obligations and liabilities as a holder of Ordinary Shares except as set out below:

- a holder of Non-Voting Ordinary Shares shall, in relation to the Non-Voting Ordinary Shares held by such holder, have no right to receive notice of, or to attend or vote at, any general meeting of shareholders (save in relation to a variation of class rights of the Ordinary Shares); and
- the Non-Voting Ordinary Shares shall be non-transferrable.

A holder of the Non-Voting Ordinary Shares may elect to have some or all of such holder’s Non-Voting Shares redesignated as Ordinary Shares by providing a written notice in a form reasonably acceptable to the Company, specifying the number of Non-Voting Ordinary Shares it wishes to have redesignated as Ordinary Shares. Upon the redesignation of the Non-Voting Ordinary Shares to Ordinary Shares, such Ordinary Shares shall rank *pari passu* with the other Ordinary Shares of the Company in all respects. The holders of Non-Voting Shares are subject to certain ownership restrictions as described in the Securities Purchase Agreement, dated March 6, 2023, including that no purchaser of Non-Voting Ordinary Shares may redesignate such shares if the holder would own in excess of 19.99% of the number of Ordinary Shares (including Ordinary Shares that may be represented by ADSs) outstanding immediately after giving effect to such redesignation.

At the Company's Annual General Meeting of Shareholders in June 2021, the Company received authority to allot up to a maximum nominal value of £13,023,851.50 to any new shares (including both Ordinary Shares and Non-Voting Ordinary Shares). As of March 31, 2023, the Company had 16,613,400 Ordinary Non-Voting shares issued and outstanding and had 167,642,959 Ordinary Shares issued and outstanding. As of March 31, 2023, the Company has a remaining nominal value of £6,986,211.70 it can issue in any new shares under the June 2021 authority.

Holders of Ordinary Shares may convert such shares to ADSs. The ADSs are listed on The Nasdaq Capital Market, and each ADS represents ten Ordinary Shares.

To date, the Company has not declared any dividends. Under 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, the Company must have distributable profits before declaring and paying a dividend.

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. As of March 31, 2023, there were 248,750 ordinary shares available for grant under the 2018 Plan, 726,940 ordinary shares available for grant under the Inducement Plan, and 627,677 ordinary shares available for grant under the ESPP.

The numbers of options and restricted stock units, the weighted average grant date fair values per stock option and per share, and the weighted average exercise prices are all shown below on a per ordinary share basis. The Company's ADSs that are listed on the NASDAQ Capital Market each represent ten ordinary shares.

Share option activity

The following table summarizes option activity for ordinary shares under the plans for the three months ended March 31, 2023:

	Shares	Weighted Average Exercise Price per Ordinary Share
Outstanding at December 31, 2022	16,424,167	$ 1.56
Granted	4,310,330	0.49
Exercised	(332,180)	0.12
Forfeited	(577,990)	5.66
Outstanding at March 31, 2023	19,824,327	$ 1.23
Vested and expected to vest at March 31, 2023	19,824,327	$ 1.23
Exercisable at March 31, 2023	9,206,850	$ 1.99

The total intrinsic value of options exercised was $0.1 million for the three months ended March 31, 2023 and 2022, respectively. The weighted-average grant date fair value of ordinary share options granted during the three months ended March 31, 2023 and 2022, was $0.49 and $0.79 per ordinary share, respectively.

Restricted share units

Performance-based restricted share units

In April 2020, the Company granted 195,000 performance-based restricted share units restricted share units ("RSUs") with a total grant date fair value of $1.4 million to its Chief Executive Officer, Bobby Gaspar, M.D., Ph.D. Dr. Gaspar earns one-third of the award for each of the first three to occur of four milestones (65,000 RSUs are earned for each achieved milestone). The milestones relate to specific clinical and regulatory goals which have to be achieved before December 31, 2023 in order for the underlying RSUs to be eligible to vest. Vesting for any earned shares occurs on January 2, 2024, so long as Dr. Gaspar remains continuously employed with the Company through that date. The Company determined that two of the milestones were probable of being achieved and recognized stock-compensation expense of $0.7 million in the three months ended March 31, 2023.

Time-based restricted share units

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

Restricted share unit activity

The following table summarizes award activity for the three months ended March 31, 2023:

	Performance-based RSUs	Time-based RSUs	Total RSUs	Weighted Average Grant Date Fair Value per Share
Unvested at December 31, 2022	195,000	1,868,876	2,063,876	$ 0.55
Granted	—	1,700,200	1,700,200	0.46
Vested	—	(600,840)	(600,840)	0.52
Forfeited	—	(53,590)	(53,590)	0.46
Unvested at March 31, 2023	195,000	2,914,646	3,109,646	$ 0.51

Share-based compensation expense

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

	Three Months Ended	
	2023	2022
Research and development	$ 1,236	$ 1,962
Selling, general and administrative	2,276	2,698
Total	$ 3,512	$ 4,660

Total share-based compensation by award type was as follows (in thousands):

	Three Months Ended	
	2023	2022
Share options	$ 2,555	$ 4,497
Restricted share units	957	163
Total	$ 3,512	$ 4,660

As of March 31, 2023, total unrecognized compensation cost related to options was $12.6 million. This amount is expected to be recognized over a weighted average period of 2.82 years. As of March 31, 2023, total unrecognized compensation cost related to time-based RSUs was $1.4 million. This amount is expected to be recognized over a weighted average period of 2.34 years. As of March 31, 2023, the total unrecognized compensation cost related to performance-based RSUs for which vesting was deemed probable was $0.2 million, which is expected to be recognized over a period of 0.8 years. As of March 31, 2023, the total unrecognized compensation cost related to performance-based RSUs for which vesting was deemed not probable was $0.5 million, the timing of recognition will be dependent upon achievement of remaining milestones.

10. Private placement transaction

On March 6, 2023, the Company entered into a Securities Purchase Agreement (“SPA” or "PIPE") with several investors, pursuant to which the Company agreed to sell, in an unregistered offering (the “2023 Private Placement”), up to an aggregate of (i) 99,166,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share (collectively, the “Shares”) and (ii) warrants to purchase an aggregate of 109,083,590 Shares. The 2023 Private Placement consists of two closings. At each closing, the Shares will be sold in fixed combinations with the warrants as units, with each unit consisting of 10 Shares and 1 accompanying warrant to purchase eleven (11) Shares. The warrants are contingently exercisable for 30 days following (i) the Company’s public announcement of its receipt of marketing approval of its biologics license application submitted to the FDA with respect to OTL-200 (the “Vesting Event”) and (ii) receipt of shareholder approval to increase the number of authorized shares. Each warrant will have an exercise price equal to $1.10 per Share in the event the Vesting Event occurs on or prior to December 31, 2024, and $0.95 per Share in the event the Vesting Event occurs after December 31, 2024. The warrants will expire at the conclusion of the 30-day exercise period or, if the Vesting Event does not occur, on March 10, 2026. Each warrant holder has the option, in their sole discretion, to exercise the warrants for either ordinary shares or non-voting ordinary shares.

On March 10, 2023, the Company completed the initial closing and issued and sold (i) 40,053,500 ordinary shares, (ii) 16,613,400 non-voting ordinary shares, and (iii) warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per unit, generating gross proceeds of $34.0 million, before deducting offering expenses of $0.9 million payable by the Company. The warrants issued in the first closing of the 2023 Private Placement are referred to collectively herein as the “PIPE Warrants”.

In addition, the Company agreed to sell and issue in the second closing of the 2023 Private Placement (i) 17,500,000 ordinary shares, (ii) 25,000,000 non-voting ordinary shares, and (iii) warrants to purchase an aggregate of 46,750,000 ordinary shares or non-voting ordinary shares, at a purchase price of $8.00 per unit (collectively, the “PIPE Units”). The second closing is contingent upon (x) the Company’s announcement of its intention to file a biologics license application (“BLA”) submission following receipt of the minutes from the U.S. Food and Drug Administration (“FDA”) in connection with the Company’s pre-BLA meeting for OTL-200, provided such minutes do not expressly advise the Company not to proceed with a BLA submission, and (y) shareholder approval to increase the number of authorized shares.

Accounting Analysis

Upon execution of the SPA on March 6, 2023, the Company determined that each of the instruments to be issued in the first and second closings did not meet the criteria for equity classification as they were not considered indexed to the Company’s stock. The

Company recorded these instruments at a fair value of $34.0 million, which was composed of $27.5 million, $6.4 million, and $0.02 million allocated to the ordinary shares, PIPE Warrants, and PIPE Units, respectively. The Company incurred issuance costs of $0.5 million in connection with executing the SPA, which were expensed upon execution within other income (expense) on the condensed consolidated statements of operations and comprehensive loss.

Upon the closing of the SPA on March 10, 2023, the Company determined that the ordinary shares met the criteria for equity classification. The PIPE Warrants issued in the first closing and the PIPE Units that may be issued in a second closing did not meet the criteria for equity classification due to the lack of sufficient authorized and unissued shares and the price adjustment feature depending on the timing of the occurrence of a Vesting Event. The Company reclassified the ordinary shares to equity and recorded a mark-to-market adjustment of a $3.6 million gain, which represents the change in fair value of the ordinary shares between March 6, 2023, and March 10, 2023. As a result of the closing, the Company recorded $24.0 million to equity. The Company incurred issuance costs of $1.1 million which were contingent on the closing of the SPA. These issuance costs were allocated between the ordinary shares, PIPE Warrants, and PIPE Units, on a relative fair value basis. Issuance costs of $0.9 million allocated to the ordinary shares were recognized as a discount to the ordinary shares recorded in permanent equity. Issuance costs of $0.2 million allocated to the PIPE Warrants and PIPE Units were expensed within other income (expense) on the condensed consolidated statement of operations and comprehensive loss.

The PIPE Warrants are classified within non-current liabilities on the condensed consolidated balance sheets as of March 31, 2023, and will be adjusted to fair value at each subsequent balance sheet date until the warrants are reclassified to equity or settled. Changes in the fair value of the PIPE Warrants are recognized as a component of other income (expense) in the condensed consolidated statement of operations and comprehensive loss. For the quarter ended March 31, 2023, the Company recognized changes in fair value resulting in a net gain of $0.3 million related to the PIPE Warrants. As of March 31, 2023, warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares were issued and outstanding and none were exercisable.

The PIPE Units are classified within non-current liabilities on the condensed consolidated balance sheets as of March 31, 2023, and will be adjusted to fair value at each subsequent balance sheet date until the units are reclassified to equity or the second closing occurs. Changes in the fair value of the PIPE Units are recognized as a component of other income (expense), net in the condensed consolidated statement of operations and comprehensive loss. For the quarter ended March 31, 2023, the Company recognized changes in fair value resulting in a net gain of $0.02 million related to the PIPE Units.

11. Restructuring charges

On March 30, 2022, the Company announced its commitment to focus on severe neurometabolic diseases and early research programs, and to discontinue its investment in and seek strategic alternatives for the Company’s programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich syndrome (“WAS”), OTL-102 for treatment of X-linked chronic granulomatous disease (“X-CGD”), and Strimvelis for adenosine deaminase severe combined immunodeficiency (“ADA-SCID”). The Company recognized a one-time charge in the first quarter of 2022 of approximately $2.5 million, which relates to employee-related termination costs. For the quarter ended March 31, 2022, approximately $2.1 million and $0.4 million is recognized in research and development expenses and selling, general, and administrative expenses, respectively, on the Company's condensed consolidated statements of operations and comprehensive loss. The restructuring charge was included in accrued expenses and other current liabilities in the Company’s condensed consolidated balance sheets.

Activity for the quarter is summarized as follows (in thousands):

	Three Months Ended March 31, 2022
Balance at beginning of period	$ 6
Charged to expense	2,481
Payments made	(6)
Balance at end of period	$ 2,481

There was no restructuring activity in the three months ended March 31, 2023.

12. Product revenue, net

The following table presents the Company's net revenue by product (in thousands):

	Three Months Ended March 31,	
	2023	2022
Libmeldy	$ 534	$ 5,059
Strimvelis	—	—
Total	$ 534	$ 5,059

Activity in each of the product revenue allowance and reserve categories for Libmeldy is summarized as follows (in thousands):

	Trade discounts and allowances	Government rebates	Total
Balance as of December 31, 2022	$ 4,390	$ 2,300	$ 6,690
Provision Related to sales in the current year	2,954	—	2,954
Credits and payments made during the period	(7,344)	—	(7,344)
Foreign currency translation	—	49	49
Balance as of March 31, 2023	$ —	$ 2,349	$ 2,349

The total reserves described above are summarized as components of the Company's consolidated balance sheets as follows (in thousands):

	As of March 31, 2023	As of December 31, 2022
Reduction of accounts receivable, net	$ —	$ 4,390
Component of accrued expenses and other current liabilities	2,349	2,300
Total revenue-related reserves	$ 2,349	$ 6,690

13. Collaboration revenue

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

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

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

The Company also entered into a Share Purchase Agreement with Pharming on July 1, 2021 (the “SPA”), pursuant to which the Company issued 1,227,738 ordinary shares to Pharming for total consideration of $7.5 million. The consideration is payment for the fair value of ordinary shares with a fair value of $4.1 million plus a $3.4 million premium on the fair value of the Company’s ordinary shares. The “Collaboration Agreement” and the “SPA” are referred to together as the “Pharming Agreements.”

Accounting Analysis

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 1,227,738 of the Company’s ordinary shares as part of the SPA, and the license and collaboration agreement, which conveys the license and provides for the Company to provide research, development, manufacturing services for OTL-105. The Pharming Agreements were entered into concurrently as part of a single commercial objective and the Company considers them a single arrangement for accounting purposes. The total upfront payments of $17.5 million are comprised of $4.1 million attributed to the equity sold to Pharming and $13.4 million attributed to the Collaboration Agreement.

The Company has concluded that the conveyance of the license for the HAE program and the provision of research, development, and manufacturing services for the HAE program represent a series of distinct services that are accounted for as a single performance obligation within the Collaboration Agreement.

The Company determined that the transaction price includes: the $13.4 million attributed to the Collaboration Agreement and the variable consideration for estimated reimbursement payments at agreed upon contractual rates to be received from Pharming for the Company’s on-going research, development, and manufacturing services. The potential future variable consideration is associated with the reimbursement for research, development, and manufacturing services provided by the Company to Pharming at agreed upon contractual rates which is the only remaining unsatisfied performance obligation. The milestone payments included in the

Collaboration Agreement are fully constrained as a result of the uncertainty regarding whether any of the associated milestones will be achieved. The Company re-evaluates the transaction price as of the end of each reporting period.

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

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

	Three Months Ended March 31,	
	2023	2022
Reimbursement revenue	$ 597	$ 400
Upfront and milestone payment revenue	106	65
Total	$ 703	$ 465

The Company had none and $0.5 million due from Pharming included in accounts receivable as of March 31, 2023, and December 31, 2022, respectively.

As of March 31, 2023, the Company had contract liabilities of $11.4 million, which is classified as either current or long-term deferred revenue in the condensed consolidated balance sheets based on the period over which this is expected to be recognized. The deferred revenue balance represents the portion of the upfront payments received related to the performance obligation that remains partially unsatisfied as of March 31, 2023.

14. Income taxes

The Company recorded an income tax benefit of $12 thousand and an income tax expense of $58 thousand for the three months ended March 31, 2023 and 2022, respectively. The Company records no income tax benefits for the net operating losses incurred in each period in the U.K due to the uncertainty regarding the realizability of the deferred tax asset. The Company's income tax relates to its subsidiaries in Europe and the U.S. The Company's income tax computed at its effective income tax rate for the three months ended March 31, 2023 and 2022, differed from income taxes computed at the U.K. statutory tax rate primarily due to the U.S. deduction for foreign derived intangible income, U.S. tax credits, and share-based compensation.

15. 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, 2023 (amounts in thousands):

Due in:	Product manufacturing commitments	Dedicated manufacturing and development resources	Exclusive transduction suites	Total AGC Commitment
2023 (remaining nine months)	$ 1,469	$ 4,299	$ —	$ 5,768
2024	1,959	5,732	2,177	9,868
2025	980	2,866	1,088	4,934
Total manufacturing commitments	$ 4,408	$ 12,897	$ 3,265	$ 20,570

Tabular disclosure above has been translated to U.S. Dollar, from Euro, using the period end exchange rate of €1.00 to $1.09.

Indemnification agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners, and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and senior management that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations in its consolidated financial statements as of March 31, 2023.

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 Form 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 for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Business overview

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

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

We have incurred significant operating losses since our inception. With the approval of Libmeldy in Europe, we are now transitioning from a primarily clinical development stage company to a commercial stage company. We plan to continue the implementation of our commercialization plan for Libmeldy and our near-term plans for commercialization include:

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

Our net losses were $17.4 million and $44.3 million for the three months ended March 31, 2023 and 2022, respectively. As of March 31, 2023, we had an accumulated deficit of $918.3 million. As of March 31, 2023, we had cash, cash equivalents and marketable securities of $146.3 million. Our losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations.

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

Recent developments

In March 2022, we announced our decision to focus on severe neurometabolic diseases and early research programs, and to discontinue our investment in and seek strategic alternatives for our programs in rare primary immune deficiencies, including OTL-103 for treatment of WAS, OTL-102 for treatment of X-CGD and Strimvelis. In connection with this new strategic focus, we reduced our workforce by approximately 30%.

In March 2023, we announced a private placement pursuant to which we agreed to sell ordinary shares, non-voting ordinary shares, and warrants to purchase ordinary shares or non-voting ordinary shares. The private placement consists of two closings. We completed the initial closing in March 2023 and sold 56,666,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share, and warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per

ten shares and accompanying warrant to purchase eleven shares. The completion of the initial closing resulted in gross proceeds of $34.0 million. Refer to the Liquidity section below for further information on the private placement.

Also in March 2023, we notified MidCap Financial of our voluntarily cancellation of the remaining commitments of $67.0 million under the Amended Credit Facility. In exchange for this cancellation, MidCap agreed to waive certain restrictive covenants of the Amended Credit Facility related to our ability to dispose of intellectual property related to deprioritized programs.

Business update regarding COVID-19

The COVID-19 pandemic presented substantial public health and economic challenges around the world, and it will likely continue to affect our business. In addition to general macro-economic effects of the pandemic, our business faced several specific challenges. For example, many of our clinical sites devoted, and continue to devote, significant resources to patients with COVID-19. If there is a future rise in hospitalizations, our clinical sites may need to dedicate additional resources to treating these people, which could limit their ability to enroll additional patients in clinical trials, if necessary.

In addition, during the pandemic, many of our employees spent time working from home due to limitations on travel and other social distancing measures. Currently, a majority of employees are on a hybrid-working model, meaning they perform part of their work in the office and part of their work outside of the office. This could increase our cybersecurity risk and hinder our ability to onboard new employees.

It is possible that if additional variants of the virus proliferate, our third-party vendors and contract manufacturers could face delays and may struggle to operate at expected levels. While we don't currently anticipate any interruptions to our business, we cannot predict this.

Finally, if there are future disruptions to the capital markets as a result of the pandemic, it could impact our ability to raise capital.

For additional information on the various risks posed by the COVID-19 pandemic, please see the section titled "Item 1A. Risk Factors" included in this Quarterly Report on Form 10-Q.

Components of our results of operations

Product revenue, net

We recognize product revenue, net, from sales of Libmeldy and Strimvelis in Europe. Product revenue is recorded net of estimates of variable consideration. Please read Note 2, Product revenue, net, to the condensed consolidated financial statements included in this Form 10-Q for further details of the reserves recorded for variable consideration. We expect that future sales of Libmeldy will fluctuate quarter over quarter. Strimvelis is distributed exclusively at the San Raffaele Hospital in Milan, Italy. We announced in March 2022 that we would discontinue our investment in and seek alternatives for Strimvelis.

Collaboration revenue

We recognize collaboration revenue under our collaboration agreement with Pharming. Under revenue recognition guidance, we account for our obligations to provide the license and research, development, and manufacturing services under the agreement as a series of distinct services that are accounted for as a single performance obligation. We recognize revenue using the cost-to-cost input method, which we believe best depicts the transfer of control to the customer. Under the cost-to-cost input method, the extent of progress towards completion is measured based on the ratio of actual costs incurred to the total estimated costs expected upon satisfying the identified performance obligation. Revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. The impact of any adjustment related to the estimated transaction price on revenue recorded to date is recognized in the period the adjustment is identified. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred. Refer to Note 2 and Note 13 to the condensed consolidated financial statements included in this Form 10-Q for further discussion on our revenue recognition around this agreement.

Cost of product sales

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

A portion of our inventory includes raw materials that were expensed prior to approval of Libmeldy, referred to as zero cost inventories. Cost of sales for newly launched products will not include the full cost of manufacturing until the initial pre-launch inventory is depleted, and additional inventory is purchased, manufactured and sold. Therefore, the cost of product sales reflects a portion but not all of the manufacturing costs of our products.

Operating expenses

Research and development expenses

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

- expenses incurred under agreements with third parties, including contract research organizations (CROs) that conduct research, pre-clinical activities and clinical trials on our behalf as well as contract manufacturing organizations that manufacture lentiviral vectors and cell-based drug products for use in our pre-clinical and clinical trials;
- expenses to acquire technologies to be used in research and development;
- salaries, benefits and other related costs, including share-based compensation expense, for personnel engaged in research and development functions;
- costs related to research and development associated with the Company's collaboration with Pharming;
- costs of outside consultants, including their fees, share-based compensation and related travel expenses;
- the costs of laboratory supplies and acquiring, developing and manufacturing pre-clinical study and clinical trial materials;
- costs related to compliance with regulatory requirements;
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities, costs related to our collaboration agreements, and other operating costs;
- upfront, milestone and management fees for maintaining licenses under our third-party licensing agreements; and
- grant awards or other government incentives unrelated to income taxes that we earn that are recorded as an offset to the related research and development costs incurred.

We expense research and development costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid expenses or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. Amortization of the Strimvelis loss provision is also recorded as an offset to research and development expense.

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and contract manufacturing organizations in connection with our 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.

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. Selling, general and administrative expenses also include distributor-related fees related to product sales analogous to a commission in arrangements where the distributor is considered to be an agent.

Other income (expense), net

Interest income

Interest income consists of income earned on our cash and cash equivalents and marketable securities.

Interest expense

Interest expense consists of interest associated with our Credit Facility with MidCap Financial, which we entered into in May 2019, and amended and restated in May 2021. The Amended Credit Facility bears a variable interest rate of 5.95% above SOFR plus a

0.10% annual increase to the annual variable interest rate, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

Other expense, net

Other expense, net consists of realized and unrealized foreign currency transaction gains and losses as well as changes in fair value of the PIPE Warrant and PIPE Unit liabilities (refer to Footnote 10 for further discussion).

Results of operations

Comparison of the three months ended March 31, 2023 and 2022

The following table summarizes our results of operations for the three months ended March 31, 2023 and 2022:

	Three Months Ended March 31,		
	2023	2022	Change
Product revenue, net	$ 534	$ 5,059	$ (4,525)
Collaboration revenue	703	465	238
Total revenues	1,237	5,524	(4,287)
Costs and operating expenses			
Cost of product revenue	367	1,571	(1,204)
Research and development	15,993	28,234	(12,241)
Selling, general and administrative	11,135	13,299	(2,164)
Total costs and operating expenses	27,495	43,104	(15,609)
Loss from operations	(26,258)	(37,580)	11,322
Other (expense) income:			
Interest income	1,029	69	960
Interest expense	(957)	(675)	(282)
Changes in fair value of PIPE Warrant and PIPE Unit liabilities	3,852	—	3,852
Other (expense) income, net	4,910	(6,052)	10,962
Total other (expense) income, net	8,834	(6,658)	15,492
Net loss before income tax	(17,424)	(44,238)	26,814
Income tax (expense) benefit	12	(58)	70
Net loss attributable to ordinary shareholders	$ (17,412)	$ (44,296)	$ 26,884

Product revenue, net

The table below summarizes our revenue earned by product (in thousands):

	Three Months Ended March 31,		
	2023	2022	Change
Libmeldy	$ 534	$ 5,059	$ (4,525)
Strimvelis	—	—	—
Total product revenue, net	$ 534	$ 5,059	$ (4,525)

Libmeldy received approval from the European Commission in December 2020, and we made our first commercial sales of Libmeldy in the first quarter of 2022. We announced in March 2022 that we would discontinue our investment in and seek alternatives for Strimvelis.

Collaboration revenue

During the three months ended March 31, 2023 and 2022, we recognized revenue of $0.7 million and $0.5 million, respectively, under our collaboration agreement with Pharming. We recognize revenue using the cost-to-cost input method. Under this method, revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred.

Cost of product sales

Cost of sales for the three months ended March 31, 2023, consisted of costs to manufacture, distribute and administer Libmeldy and Strimvelis and royalty payments due to third parties related to these sales. The gross margin on our product revenue, net for the three months ended March 31, 2023, was enhanced by our use of zero cost inventories. Utilizing the per unit average cost of materials that

were purchased prior to approval and expensed that were utilized in the manufacturing process for our products sold during the period, cost of product sales for the three months ended March 31, 2023, would have been approximately $0.6 million.

Research and development expenses

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

	Three Months Ended March 31,		
	2023	2022	Change
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 5,293	$ 7,058	(1,765)
Primary immune deficiencies	—	3,483	(3,483)
Blood disorders	—	2,503	(2,503)
Other research and pre-clinical programs under development	321	1,090	(769)
Total direct research and development expenses	5,614	14,134	(8,520)
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	6,763	8,933	(2,170)
Share-based compensation	1,236	2,155	(919)
Restructuring costs	—	2,064	(2,064)
Accretion of Strimvelis loss provision	—	(274)	274
Research and development tax credit	(769)	(3,337)	2,568
Facility and other	3,149	4,559	(1,410)
Total indirect research and development expenses	10,379	14,100	(3,721)
Total research and development expenses	$ 15,993	$ 28,234	(12,241)

Total direct research and development expenses decreased from $14.1 million for the three months ended March 31, 2022, to $5.6 million for the three months ended March 31, 2023. The $8.5 million decrease, or -60%, was primarily the result of:

- a $3.5 million decrease in costs associated with primary immune deficiencies programs, a $2.5 million decrease associated with blood disorder programs, and a $0.8 million decrease in other research and pre-clinical programs due to de-prioritization of and decreased investment in these programs after the strategic restructuring efforts announced in March 2022; and
- a $1.8 million decrease in spending on neurometabolic disorder programs, specifically driven by decreased spending on OTL-200 for MLD as we reduced our clinical expenditures for that program after the commercial launch of Libmeldy in the first quarter of 2022.

Total indirect research and development expenses decreased from $14.1 million for the three months ended March 31, 2022, to $10.4 million for the three months ended March 31, 2023. The $3.7 million decrease, or -26%, was the result of:

- a $2.2 million decrease in personnel related costs, a $0.9 million decrease in share-based compensation costs, and a $1.4 million decrease in facility and other costs related to our strategic restructuring efforts announced in March 2022 and associated employee terminations;
- a $2.1 million decrease in restructuring costs as we did not have any restructuring efforts in 2023; and
- a $2.6 million decrease in the UK research and development tax credit, which is an offset to research and development expenses incurred for qualifying programs. This decrease was driven by lower qualifying costs incurred during the quarter.

Selling, general and administrative expenses

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

	Three Months Ended March 31,		
	2023	2022	Change
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 3,723	$ 4,629	(906)
Share-based compensation	2,276	2,698	(422)
Restructuring costs	—	417	(417)
Consulting, professional, and insurance-related costs	2,609	3,464	(855)
Marketing, promotions, and advocacy	838	773	65
Facilities and other costs	1,689	1,318	371
Total selling, general, and administrative expenses:	$ 11,135	$ 13,299	$ (2,164)

Selling, general and administrative expenses decreased from $13.3 million for the three months ended March 31, 2022, to $11.1 million for the three months ended March 31, 2023. The $2.2 million decrease, or -16%, was a result of:

- a $0.9 million decrease in personnel related expenses and a $0.4 million decrease in share-based compensation expenses due to decreased headcount as a result of the strategic restructuring announced in 2022;
- a $0.9 million decrease in consulting, professional, and insurance related costs due to lower insurance premium costs and legal fees incurred in 2023;
- a $0.4 million decrease restructuring costs due to no restructuring activities in 2023; and
- a $0.4 million increase in facilities and other costs driven by higher shareholder and ADS administration costs.

Other income (expense), net

Other (expense) income, net, increased from a $6.7 million loss for the three months ended March 31, 2022, to an $8.8 million gain for the three months ended March 31, 2023. During the three months ended March 31, 2023, we had net realized and unrealized gains on foreign currency transactions of $5.6 million, comprised primarily of unrealized losses, compared to net realized and unrealized losses of $6.1 million for three months ended March 31, 2022. Unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar, Pounds sterling, and Euro exchange rates.

Interest expense was $1.0 million and $0.7 million for the three months ended March 31, 2023 and 2022, respectively. Interest income was $1.0 million and $0.1 million for the three months ended March 31, 2023 and 2022, respectively. The increase to both interest expense and interest income is attributable to interest rate increases throughout 2022 driven by anti-inflationary measures born from the current economic environment.

In the three months ended March 31, 2023, we incurred a $3.9 million gain relating to the fair value remeasurements of our PIPE Warrant and PIPE Unit liabilities from the announcement date of March 6, 2023, to the closing date of March 10, 2023, and from the closing date to March 31, 2023. No such changes were recorded in 2022.

Liquidity and capital resources

From our inception through March 31, 2023, we have not generated significant revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We acquired Strimvelis and the program that is now Libmeldy from GSK in April 2018, and our product candidates are in various phases of preclinical and clinical development. In December 2020, the European Commission granted standard marketing authorization for Libmeldy. We launched Libmeldy in Europe and generated our first commercial sale in the first quarter of 2022. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our IPO and follow-on offering, proceeds from the sale of ordinary shares in our private placement, proceeds from the sale of convertible preferred shares, proceeds associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit (“SME”) program and the Research and Development Expenditure (“RDEC”) program, reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine (“CIRM”), upfront payments from our collaboration agreement with Pharming Group N.V., our Original Credit Facility and our Amended Credit Facility, and through proceeds from sales of Libmeldy in Europe beginning in 2022.

On February 27, 2020, we entered into a Sales Agreement with Cowen and Company, LLC (“Cowen”), as agent, relating to an “at the market offering,” pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price

of up to $100.0 million. On March 24, 2022, we delivered written notice to Cowen to terminate the Sales Agreement, effective as of March 30, 2022, pursuant to Section 11(b) thereof. Prior to termination, we had not sold any ADSs pursuant to the Sales Agreement. As a result of the termination of the Sales Agreement, we will not offer or sell any ADSs under the Sales Agreement. On October 6, 2022, we entered into a Sales Agreement with Guggenheim Securities, LLC, as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $30.0 million. As of March 31, 2023, we have not sold any shares under the Guggenheim Sales Agreement.

On March 6, 2023, we announced a private placement pursuant to which we agreed to sell up to an aggregate of 99,166,900 ordinary shares and non-voting ordinary shares, nominal value of £0.10 per share, and warrants to purchase an aggregate of 109,083,590 ordinary shares or non-voting ordinary shares. The private placement consists of two closings. At each closing, the shares will be sold in fixed combinations with the warrants and units, with each unit consisting of 10 shares and 1 accompanying warrant to purchase 11 shares. We received approximately $34 million at the initial closing on March 10, 2023. We may receive an additional $34 million from the second closing of the private placement. This second closing is conditioned upon (i) our announcement of our intention to file a biologics license application ("BLA") submission following receipt of the minutes from the U.S. Food and Drug Administration ("FDA") in connection with our pre-BLA meeting for OTL-200, provided such minutes do not expressly advise the Company not to proceed with a BLA submission, and (ii) receipt of approval from the our shareholders, to be provided at a meeting of shareholders no later than 120 days after the initial closing, to give the Company's directors authority to issue the securities to be issued and sold in the second closing of the private placement and the shares issuable upon exercise of the warrants to be issued and sold in the private placement.

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

Cash flows

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

	Three Months Ended March 31,	
	2023	2022
Net cash used in operating activities	$ (29,508)	$ (19,599)
Net cash provided by (used in) investing activities	(9,346)	25,107
Net cash provided by (used in) financing activities	31,506	—
Effect of exchange rate changes on cash	411	(645)
Net increase (decrease) in cash, cash equivalents, and restricted cash	$ (6,937)	$ 4,863

Operating activities

Net cash used in operating activities for the three months ended March 31, 2023, was $28.6 million and was primarily driven by our net loss of $17.4 million, partially offset by non-cash charges consisting of depreciation and amortization of $0.6 million, share based compensation of $3.5 million, gain on the change in fair value of the PIPE Warrant and PIPE Unit liabilities of $3.8 million, and unrealized foreign currency transaction gains on intercompany accounts of $6.2 million. Our net cash used in operating activities also included a net use of cash of $6.0 million related to changes in operating assets and liabilities as follows:

- a net source of cash of $8.6 million related to the collection of previously outstanding receivables from product sales;
- a net use of cash of $7.9 million related to changes in accounts payable, accrued expenses, and other current liabilities primarily driven by payment of employee bonuses;
- a net use of cash of 4.1 million from an increase in prepaid expenses, other current assets, and other assets primarily due to payment for various vendor services in advance of them being performed;
- a net use of cash of $1.6 million related to annual rent payments for our suite space with AGC Biologics; and
- a net use of cash of $0.8 million related to the UK research and development tax credit primarily due to timing of aggregation of the 2023 receivable and its payout.

During the first quarter of 2022, operating activities used $19.6 million of cash, primarily resulting from our net loss of $44.3 million. Cash provided by changes in our operating assets and liabilities was $12.6 million, which was primarily driven by a decrease in our research and development tax credit receivable of $13.5 million and $1.5 million of right-of-use lease assets offset by a $2.7 million increase in accounts receivable and decrease in lease liabilities of $3.4 million. Non-cash adjustments to operating activities of $15.7 million was generally due to $4.7 million in non-cash share-based compensation expense, and unrealized foreign currency transaction gains on investments and intercompany accounts by our UK subsidiary of $1.4 million, which are an add-back to cash flows from operating activities.

Investing activities

Net cash used in investing activities for the three months ended March 31, 2023, was $9.3 million. This net cash provided by investing activities was primarily driven by proceeds from the sales and maturities of marketable securities that we utilize for operating activities, offset by purchases of property and equipment.

During the three months ended March 31, 2022, net cash provided by investing activities was $25.1 million, primarily driven by proceeds from the sales and maturities of marketable securities that we utilize for operating activities.

Financing activities

During the three months ended March 31, 2023, net cash provided by financing activities was $31.5 million, consisting primarily of cash generated from our private placement financing of $34.0 million, offset by payments of principal on our note payable of $2.4 million.

We had no cash provided by or used in financing activities for the three months ended March 31, 2022.

Funding requirements

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

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

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even though we started generating Libmeldy product sales in 2022, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe our existing cash, cash equivalents, and marketable securities on hand, together with expected proceeds from sales of Libmeldy, will enable us to fund our operating expenses and capital expenditure requirements into 2025. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

Critical Accounting Policies and Estimates

Our 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
- Product revenue, net - Libmeldy

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, 2022.

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, 2023, we had cash, cash equivalents, marketable securities, and restricted cash of $150.5 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 $33.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 5.95% plus SOFR plus a 0.10% annual increase to the variable interest rate. As of March 31, 2023, the carrying value of the term loans under the credit facility was $30.1 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 $5.6 million and losses of $6.1 million for the three months ended March 31, 2023 and 2022, respectively. These foreign currency transaction losses are primarily related to revaluation of intercompany balances that are denominated in U.S. dollar that are recorded on entities whose functional currency is not 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, 2023, our disclosure controls and procedures were effective at a 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, 2023, 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, 2023, we were not a party to any material legal proceedings.

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 Annual Report and in our other SEC filings. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and prospects. This Quarterly Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in forward-looking statements as a result of certain factors, including the risks described below and elsewhere in this 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 $17.4 million and $44.3 million for the three months ended March 31, 2023 and 2022, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares, through sales of our ADSs in our initial public offering and follow-on offering, and through private placements of our ordinary shares. We have devoted substantially all of our efforts to research and development, including clinical and pre-clinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Libmeldy in the European Union, building a global commercial infrastructure to support commercialization of Libmeldy (OTL-200) and our product candidates if such product candidates are approved, as well as to building our team. Absent the realization of sufficient revenue from product sales of Libmeldy and from sales of our current or future product candidates, if approved, we may never attain profitability.

We expect to continue to incur significant expenses and operating losses for the foreseeable future, particularly if, and as, we:

- seek marketing approvals for our product candidates that successfully complete clinical trials or meet primary endpoints, if any;
- market and sell Libmeldy in Europe and grow our commercial infrastructure for the commercialization (or anticipated commercialization) of any product candidates that we may submit for and obtain marketing approval anywhere in the world;
- continue the development of our product candidates;
- continue our ongoing clinical trials and any required regulatory updates for certain de-prioritized programs;
- conduct investigational new drug application, or IND, or clinical trial application, or CTA, enabling studies for our pre-clinical programs;
- initiate additional clinical trials and pre-clinical studies for our other product candidates or future product candidates, including new research programs in genetic subsets of frontotemporal dementia, or FTD, and Crohn's disease;
- seek to identify and develop, acquire or in-license additional product candidates or technologies;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates, to support technology and process innovation, and to support manufacturing of product to commercial scale;
- establish partnerships with contract development and manufacturing organizations, or CDMOs;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility in the long-term;
- hire and retain personnel, such as non-clinical, clinical, pharmacovigilance, quality, regulatory affairs, process development and control, manufacturing, supply chain, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- encounter delays or setbacks in the pre-clinical testing, enrollment or conduct of our clinical trials for our product candidates, encounter delays in regulatory review timelines, or experience high levels of absenteeism due to the COVID-19 pandemic;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

Since receiving marketing authorization, only a limited number of patients have been treated with Libmeldy. There is no assurance that revenue from sales of Libmeldy alone will be sufficient for us to become profitable. To become and remain profitable, we must

develop and eventually commercialize product candidates with greater market potential. This will require us to be successful in a range of challenging activities, and our expenses will increase as we seek to complete necessary pre-clinical studies and clinical trials of our product candidates, and manufacture, market and sell Libmeldy or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenue that is significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

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

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully develop and commercialize products. Although we have generated revenue from the sale of Libmeldy and Strimvelis in Europe, we will not achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. Our ability to generate future revenue from product sales depends heavily on our and or our collaborators' success in:

- completing research and pre-clinical development of our product candidates and identifying attractive new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates, including maintaining or reaching target enrollment levels and collecting the necessary follow-up data;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- successfully commercializing Libmeldy in Europe and other product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related post-marketing commitments for regulatory compliance for Libmeldy and Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Libmeldy and Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Libmeldy and Strimvelis, if sales are resumed, and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Libmeldy and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- the impact of geopolitical instability and the COVID-19 pandemic, including the emergence of new variants;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and manufacturing capabilities;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

We expect that we will continue to incur significant costs associated with commercializing Libmeldy in Europe and any other products for which we obtain marketing approval. Our expenses could increase beyond expectations if the FDA, the EMA or other regulatory authorities require us to perform clinical or other studies in addition to those that we currently anticipate or if we encounter delays or clinical holds in the development of our product candidates. Even if we generate more significant revenue from sales of Libmeldy in Europe and generate revenue from the sale of any other approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We may not receive any additional amounts under the Securities Purchase Agreement, dated March 6, 2023.

As previously disclosed, on March 6, 2023, we announced a private placement pursuant to which the Company agreed to sell ordinary shares, non-voting ordinary shares and warrants. If certain conditions are met and all warrants are exercised, the Company could receive a total of $188 million pursuant to the private placement. In accordance with the Securities Purchase Agreement (the "SPA"), the Company received $34 million at the initial closing on March 10, 2023. However, the Company may not receive any additional amounts under the SPA.

As described below, the second closing is contingent and could be delayed or never happen, and certain of the contingencies are not entirely without the Company's control. In addition, the warrants sold under the SPA do not obligate the purchasers to exercise them, and even if they are exercised, they are exercisable at a lower price if FDA approval of OTL-200 is delayed beyond 2024.

The investors in the private placement agreed to purchase additional ordinary shares, non-voting ordinary shares and warrants at a pre-agreed price at a second closing for an aggregate total of $34 million. The second closing is subject to the Company's public announcement of our intention to submit a BLA application with the FDA following receipt of minutes from the Company's pre-BLA meeting with the FDA, which was held in the second quarter of 2023. The second closing is also subject to shareholder approval for authority under U.K. law to allot the shares issuable upon exercise of the warrants and to disapply pre-emption rights in respect of such authority.

The second closing has not yet occurred, and it may never occur. The minutes from our pre-BLA meeting with the FDA may not meet the criteria to trigger the second closing, which could delay or prevent the Company from receiving additional funds pursuant to the SPA.

The second closing could also be delayed or never occur if the Company fails to receive the necessary shareholder approvals. Although we have agreed to hold a shareholder meeting no later than 120 days following the initial closing, the required shareholder votes could fail or we could fail to receive the quorum necessary to hold the vote. Under U.K. law, the proposal asking shareholders to disapply pre-emption rights is considered a special resolution requiring the affirmative vote of 75% of votes cast by shareholders present (in person or by proxy) at the meeting and entitled to vote. Under the SPA, we have agreed to continue seeking shareholder approval if the necessary votes fail for a period of time, but we may never receive the required shareholder vote.

The purchasers of warrants are not obligated to exercise the warrants, so we may not receive any additional proceeds from their exercise. The warrants will become exercisable during the 30 days following the Company's announcement of receipt of marketing approval of its BLA with respect to OTL-200; provided, that exercise of any warrant is conditioned on the receipt of shareholder approval (as described above). If the Company does not announce receipt of marketing approval of its BLA or does not receive the necessary shareholder approval, the warrants will expire on March 10, 2026. In addition, the exercise price of the warrants is lower if OTL-200 is approved by the FDA after 2024, so any proceeds we receive from their exercise could be lower than the total amount possible as of today. The exercise price of the warrants is $1.10 per ordinary share if OTL-200 is approved by the FDA in 2024 and $0.95 per ordinary share if approval comes after 2024. (Each publicly traded ADS in the Company is represented by ten ordinary shares.)

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 three months ended March 31, 2023, primarily due to our net loss of $17.4 million for that period. We expect to continue to incur substantial expenses in connection with our ongoing activities, which may increase over time, particularly as we (i) continue to commercialize Libmeldy in Europe, (ii) continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and (iii) continue to enhance and optimize our vector technology and manufacturing processes. In addition, we expect to incur significant expenses related to product sales, post-marketing regulatory commitments, medical affairs, marketing, manufacturing, distribution and quality systems to support Libmeldy and any other products for which we obtain marketing approval. Furthermore, we will continue to incur costs associated with operating as a public company, including with respect to the system and process evaluations and testing of our internal controls and financial reporting. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on reasonable terms, or at all, we would be forced to delay, reduce or eliminate certain of our ongoing activities, such as research and development programs and commercialization efforts.

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

- the success of our commercialization efforts and market acceptance of Libmeldy in Europe;
- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities to support Libmeldy in Europe and any other products for which we obtain marketing approval, including costs relating to quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution;

- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors on a timely basis for Libmeldy and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related post-marketing commitments for regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, pre-clinical development and clinical trials for our product candidates or future product candidates, including the need to conduct long-term follow-up for up to 15 years for our development programs and additional clinical trials to support marketing approvals for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Libmeldy and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

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

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

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

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

We were incorporated in August 2018 to become a holding company for Orchard Therapeutics (Europe) Limited, which was founded in 2015, and its subsidiaries. Our operations to date have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring certain of our product candidate portfolios and rights to our technology, identifying potential product candidates, undertaking pre-clinical studies and planning and supporting clinical trials of our product candidates, establishing research and development and manufacturing capabilities, establishing a quality management system, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union and building a global commercial infrastructure to

support commercialization of Libmeldy. Consequently, any predictions about our future success or viability may not be as accurate as they might be if we had a longer operating history. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and setbacks.

Unfavorable market and global economic conditions could adversely affect our business, financial condition or results of operations.

As widely reported, global credit and financial markets have experienced extreme volatility and disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, and uncertainty about economic stability, including most recently in connection with the COVID-19 pandemic, current macroeconomic conditions, currency exchange rates, and volatile financial markets. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Furthermore, our stock price may decline due in part to the volatility of the stock market and the general economic downturn.

Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay, scale back or discontinue the development and commercialization of one or more of our product candidates or delay our pursuit of potential in-licenses or acquisitions. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

Volatility among foreign currencies could impact our results of operations. As an example, we had net realized and unrealized gains on foreign currency transactions of $5.6 million during the three months ended March 31, 2023, compared to net realized and unrealized losses of $6.1 million during the three months ended March 31, 2022. Unrealized gains and losses are driven primarily by entities that have a functional currency other than the U.S. Dollar that have intercompany balances denominated in U.S. Dollar.

Adverse developments in the banking system and financial services industry, including the failure or concerns regarding the failure of banks and financial institutions, could have an adverse effect on our ability to raise additional capital and our operations and financial results.

Actual events involving limited liquidity, defaults, non-performance or other adverse developments that affect financial institutions, transactional counterparties or other companies in the financial services industry or the financial services industry generally, or concerns or rumors about any events of these kinds or other similar risks, have in the past and may in the future lead to market-wide liquidity problems. For example, the Federal Deposit Insurance Corporation was appointed as receiver of Silicon Valley Bank and Signature Bank in March 2023 and as receiver of First Republic Bank prior to its acquisition by JPMorgan in May 2023. Similar impacts have occurred in the past, such as during the 2008-2010 financial crisis. These events exposed vulnerabilities in the banking sector, including legal uncertainties, significant volatility and contagion risk, and caused instability in the market prices of regional bank stocks. The closure of financial institutions, even if such financial institutions are unrelated to our business, may result in declines in the price of our stock.

Although we did not hold cash deposits at recently closed banks, we are unable to predict the extent or nature of the impacts of these evolving circumstances at this time. If, for example, other banks and financial institutions enter receivership or become insolvent in the future in response to financial conditions affecting the banking system and financial markets, our ability to access our existing cash, cash equivalents and investments may be threatened. In addition, if any other parties with whom we conduct business are unable to access funds pursuant to such instruments or lending arrangements with such a financial institution, such parties' ability to pay their obligations to us or to enter into new commercial arrangements requiring additional payments to us could be adversely affected. While it is not possible at this time to predict the extent of the impact that the failure of these banks or the high market volatility and instability of the banking sector could have on economic activity and our business in particular, the failure of other banks and financial institutions and the measures taken by governments, businesses and other organizations in response to these events could adversely impact our business, financial condition and results of operations.

Although we continue to assess our banking relationships as we believe necessary or appropriate, our access to cash in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impaired by factors that affect the financial institutions with which we have banking relationships, and in turn, us. These factors could include, among others, events such as liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements, disruptions or instability in the financial services industry or financial markets, or concerns or negative

expectations about the prospects for companies in the financial services industry. The results of events or concerns that involve one or more of these factors, or other general impact on the financial markets or financial services industry generally, could include a variety of material and adverse impacts on our current and projected business operations and our financial condition and results of operations. These could include, but may not be limited to:

- Delayed access to deposits or other financial assets or the uninsured loss of deposits or other financial assets;
- Inability or reductions in our ability to enter into new credit facilities or other working capital resources;
- Potential or actual breach of financial covenants in our credit agreements or credit arrangements;
- Potential or actual cross-defaults in other credit agreements, credit arrangements or operating or financing agreements; or
- Termination of cash management arrangements and delays in accessing or actual loss of funds subject to cash management arrangements.

In addition, widespread investor concerns regarding the U.S. or international financial systems could result in less favorable financing terms, including higher interest rates or costs and tighter financial and operating covenants, or systemic limitations on access to credit and liquidity sources, thereby making it more difficult for us to raise additional capital on acceptable terms or at all. Any decline in available funding or access to our cash and liquidity resources could, among other risks, adversely impact our ability to meet our operating expenses, financial obligations or fulfill our other obligations, result in breaches of our financial and/or contractual obligations or result in violations of federal or state wage and hour laws. Any of these impacts, or any other impacts resulting from the factors described above or other related or similar factors not described above, could have material adverse impacts on our liquidity and our current and/or projected business operations and financial condition and results of operations.

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

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

We have concentrated our research and development efforts on our autologous *ex vivo* gene therapy approach, and our future success depends on our successful development of commercially viable gene therapy products. There can be no assurance that we will not experience problems or delays in developing new products and that such problems or delays will not cause unanticipated costs or that any such development problems can be solved. Although we have established a commercial infrastructure for the production of Strimvelis in the European Union and we are building a global commercial infrastructure to support commercialization of Libmeldy, we may experience delays in establishing a sustainable, reproducible and scalable manufacturing capability with commercial CDMO partners, which may prevent us from commercializing our product candidates for which we obtain marketing approval on a timely or profitable basis, if at all.

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

The results from our clinical trials for OTL-200 for MLD and for any of our other product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. Before we submit our product candidates for marketing approval, the FDA or the EMA may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.

The results from our clinical trials may not be sufficiently robust to support the approval of or submission of marketing approval for our product candidates, including by the FDA for OTL-200. The FDA and EMA normally require two registrational trials to approve a drug or biologic product, and therefore either the FDA or EMA might require that we conduct additional clinical trials of our product candidates prior to a BLA or MAA submission, respectively. The FDA and EMA typically do not consider a single registrational clinical trial to be adequate to serve as sufficient evidence to support a marketing authorization unless, among other things, (i) the trial is well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and (ii) a confirmatory study would be practically or ethically impossible.

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

For example, although the FDA cleared our IND application for OTL-200 in 2020 and we received Regenerative Medicine Advanced Therapy, or RMAT, designation in 2021, there can be no guarantee we will be successful in resolving open matters to the FDA's satisfaction before our BLA submission is complete.

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

In addition, data obtained from pre-clinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other foreign regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. The FDA may further refer a 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 BLA or MAA submissions. Based on this assessment, the FDA or EMA may require that we conduct additional pre-clinical studies or clinical trials prior to submitting or approving a BLA or MAA for our target indications.

It is possible that the FDA or EMA may not consider the results of our clinical trials, including reliance on foreign clinical data, to be sufficient for approval of our product candidates. If the FDA or EMA require additional trials, we would incur increased costs and delays in the marketing approval process, which may require us to expend more resources than we have available. In addition, it is possible that the FDA and EMA may have divergent opinions on the elements necessary for a successful BLA and MAA submission, respectively, which may cause us to alter our development, regulatory or commercialization strategies.

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

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

The FDA and EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as U.S. congressional committees and other governments or governing agencies, have also

expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. Adverse events in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates, which could require additional pre-clinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval. Similarly, the European Commission may issue new guidelines concerning the development and marketing authorization for gene therapies and require that we comply with these new guidelines, which could require additional pre-clinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval.

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

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

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

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

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

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

our gene therapy product candidates demonstrates adverse side effects or adverse events at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

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

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

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

Any of these events could prevent us from achieving or maintaining market acceptance of Libmeldy and any other products for which we obtain marketing approval and could significantly harm our business, prospects, financial condition and results of operations.

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

We have limited experience conducting company-sponsored clinical trials and to date most of our product candidates have been evaluated under investigator-sponsored clinical trials using drug product manufactured at the applicable or relevant academic site. We did not control the design or administration of these investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these clinical trials. Investigator-sponsored clinical trials are often conducted under less rigorous clinical and manufacturing standards than those used in company-sponsored clinical trials. For example, the drug product used in our company-sponsored clinical trials is manufactured by third party CDMOs using current good manufacturing practices, or cGMP, standards. Accordingly, regulatory authorities may closely scrutinize the data collected from these investigator-sponsored clinical trials and may require us to obtain and submit additional clinical data prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates. We will be required to demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CDMOs, and we cannot provide assurances that we will satisfy such comparability requirements. We may also be required to demonstrate improved quality and drug product manufacturing state of control in accordance with cGMP standards.

For example, in the compassionate use program conducted by Great Osmond Street Hospital, or GOSH, one patient experienced an SAE, staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. A similar SAE, bacteremia, was observed in the clinical trial conducted at University of California Los Angeles, or UCLA, for our since-returned program OTL-101 for ADA-SCID with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. The bacteremia resolved on day three without sequelae. We believe that our commercial manufacturing processes for our product candidates, together with cryopreserved formulation, which allows for safety/microbiological testing to be completed prior to drug infusion to the patient, could mitigate the risk of contamination of products that might have resulted in such infections, but there can be no assurance that this will be the case. To the extent that the results of our current company-sponsored trials are inconsistent with, or different from, the results of any

investigator-sponsored trials or raise concerns regarding our product candidates, the regulatory authorities may question the results from some or all of these trials, and may require us to obtain and submit additional clinical data from drug product manufactured by CDMOs prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates.

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

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

In those cases where clinical trials were conducted using vector or drug product manufactured at academic research centers, we will need to demonstrate comparability between vector and drug product manufactured by our CDMOs with vector or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another. In other cases, we may elect to initially seek approval of our product candidate using one cellular source only and subsequently seek approval for the use of the other cellular source. We cannot be assured that the FDA, EMA or other regulatory authority will not require us to conduct additional analytical studies (including comparability analyses), pre-clinical studies or clinical trials before approving our product candidates using these intended commercial production methods and processes. Moreover, we cannot be assured that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval of our product candidates using these production methods and processes.

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

If an adequate potency assay for a product candidate is not available, if we face delays, or if the FDA or EMA require additional tests or recommend a different approach to support the potency of any of our product candidates, regulatory approval for any such product candidates will be delayed and such regulators might request additional clinical data to support comparability analysis. Similarly, if one or more of these regulatory authorities does not accept that our drug product manufactured with HSCs derived from the patient's mobilized peripheral blood is comparable to drug product manufactured with HSCs derived from the patient's bone marrow, any regulatory approval would be limited to drug product manufactured with HSCs derived from the patient's bone marrow until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials.

Our development and commercialization efforts, respectively, may be unsuccessful.

We may spend several years and devote substantial resources to any particular current or future product candidate, and failure may occur at any stage. Further, even if we receive approval of a product candidate, we may not achieve commercial success for a variety of facts. For example, we may not achieve market acceptance in the medical community, our pricing assumptions might be wrong, and our assumptions about the size of the anticipated patient populations may prove inaccurate.

Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. For example, in May 2020, we announced our decision to reduce investment in the development of OTL-101 for treatment of adenosine deaminase severe combined immunodeficiency, or ADA-SCID, and OTL-300 for treatment of Beta-thalassemia, or TDT. We have since returned licenses to the original licensors relating to both programs. Additionally, in March 2022, we announced that we would discontinue our investment in and seek strategic alternatives for our programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich Syndrome, or WAS, OTL-102 for treatment of X-linked chronic granulomatous disease, or X-CGD, and Strimvelis.

Our focus on the advancement of our other product candidates may ultimately prove to be unsuccessful or less successful than if we had continued to prioritize such de-prioritized product candidates, and if we choose to re-prioritize such de-prioritized product candidates in the future, we may experience delays that would not have otherwise occurred, due to inefficiencies from loss of organizational knowledge and ramp up costs. Moreover, we may be unable to realize the savings we expect to achieve by de-prioritizing certain programs, which could result from, among other things, higher than expected transition or termination costs.

If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

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

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

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

From time to time, we may publish interim data or ad hoc analyses from investigator-sponsored or company-sponsored clinical trials of our product candidates. Preliminary data and ad hoc analyses from these clinical trials may change as longer-term patient data become available. In general, we seek to conduct interim analyses at times we pre-specify with the applicable regulators prior to commencement of the trial, at which time we lock and reconcile the database. We may occasionally elect not to conduct subsequent interim analyses so as not to compromise the statistical analysis plan for the trial. Accordingly, our interim analyses do not include data subsequent to the cut-off date and may not be available until the next planned interim analysis. From time to time, preliminary data and ad hoc analyses might be presented, typically by academic investigators at scientific conferences or in scientific publications.

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

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

For example, although sustained clinical activity has been observed in clinical trials to date for Libmeldy (OTL-200), follow-up in these clinical trials is ongoing and there can be no assurance that the results, in each case as of the applicable primary endpoint measurement date, seen in clinical trials of any of our product candidates ultimately will result in success in clinical trials or provide adequate support for marketing approvals by the FDA, in the case of Libmeldy, without conducting further clinical trials. This 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. Our product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in pre-clinical studies. Our product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical trials. There can be no assurance that any of these trials will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates. In addition, there can be no assurance that we will be able to achieve the same or similar success in our pre-clinical studies and clinical trials of our other product candidates.

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

A number of patients have been administered our autologous *ex vivo* gene therapies through compassionate use programs. Compassionate use is a term that is used to refer to the use of an investigational drug outside of a clinical trial to treat a patient with a

serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options. Regulators often allow compassionate use on a case-by-case basis for an individual patient or for defined groups of patients with similar treatment needs. Caution should be given when reviewing and interpreting compassionate use data. While results from treating patients through compassionate use have in certain cases been encouraging, we cannot be assured that the results observed in these cases will be observed in our ongoing or future clinical trials or that our ongoing and future clinical trials will ultimately be successful.

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

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

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields generally, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. Additionally, the COVID-19 global pandemic has had and may continue to have a sustained impact on our ability to recruit and follow-up with patients either due to continued or renewed restrictions on travel or shelter-in-place orders or policies or due to changes in patient willingness to participate in trials or travel to study sites in the wake of the pandemic. Additionally, COVID-19 related study site policies may create delays or setbacks in our ability to continue to enroll or to dose patients. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

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

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

- ability to monitor subjects adequately during and after treatment.

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

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

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

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

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and the outcome is uncertain. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable patients and in sufficient volume to participate in our clinical trials;
- imposition of a clinical hold by regulatory agencies;
- failure by our academic partners, CROs, other third parties or us to adhere to clinical trial protocol and record keeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- delays in patient enrollment, missed assessments resulting from remote follow-up visits, or delays in completion of participation as a result of the impact of the COVID-19 global pandemic or future pandemics or similar events;
- the occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete pre-clinical and clinical development could result in additional costs to us or impair our ability to generate revenue. In addition, if we make changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to

commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

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

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

We have initiated a rolling BLA for OTL-200 and may elect to initiate a rolling BLA for our other product candidates. The FDA will not complete, and may delay initiating, its review of a BLA until all required information is submitted.

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. For OTL-200, we have submitted a rolling BLA.

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

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

In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. For example, regulatory agencies may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. Regulators may approve a product candidate for a smaller patient population, drug formulation (such as drug product using HSCs derived from bone marrow as opposed to mobilized peripheral blood or vice versa) or manufacturing processes (such as fresh drug product as opposed to cryopreserved or use of different manufacturing facilities) than we are seeking. If we are delayed in obtaining or unable to obtain necessary regulatory approvals, or if we obtain more limited regulatory approvals than we expect, our business, prospects, financial condition and results of operations may suffer.

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

approvals, we or they will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

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

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

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

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

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

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by the EMA or other regulatory authorities in other countries or jurisdictions, and approval by the EMA or another regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. For example, though we received standard marketing authorization of Libmeldy (OTL-200) from the European Commission in December 2020, there is no guarantee that we will receive approval from the FDA.

Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional pre-clinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit an MAA to the EMA for approval of our product candidates in the European Union, but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process.

Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market

will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects may be harmed.

Additionally, the UK formally left the EU in January 2020. The EU and the UK have concluded a Trade and Cooperation Agreement, or TCA, which has been formally applicable since May 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products, and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore currently aligns in the most part with EU regulations, however it is possible that these regimes will diverge in the future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. For example, the new Clinical Trials Regulation, which became effective in the EU on January 31, 2022, and provides for a streamlined clinical trial application and assessment procedure covering multiple EU Member States, has not been implemented into UK law, and a separate application will need to be submitted for clinical trial authorization in the UK. The separate, and potentially diverging, regulatory regimes between Great Britain and the EU may increase our regulatory burden of applying for and obtaining authorization in Great Britain and the EU.

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

To date, most of the clinical trials conducted on our product candidates have been conducted outside the United States. Although the FDA may accept data from clinical trials conducted outside the U.S., acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept data from any trial that we conduct outside the U.S., due to study design or otherwise, it would likely result in the need for additional trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates. Further, if we do not have an IND open for a product candidate, we forego more frequent interactions and dialogue with the FDA regarding the design and conduct of our trials as well as product comparability, which may delay or halt the development of such product candidates later in development should the FDA later disagree with the design or conduct of our trials or product comparability approach.

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

While we intend to seek designations for our product candidates with the FDA and other comparable regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.

The FDA and comparable other regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. OTL-200 for MLD received RMAT designation from the FDA, and OTL-203 for MPS-IH received a Priority Medicines, or PRIME, designation from EMA. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

For example, we may seek a Breakthrough Therapy designation for some of our other product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our

product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

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

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

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

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

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

conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

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

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

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan designation in respect of a medicinal product if the sponsor can establish that such product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EU. Additionally, orphan designation may be granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely such products would generate sufficient return in the EU to justify the necessary investment their development. In either case, the applicant for orphan designation must also demonstrate that no satisfactory method of diagnosis, prevention, or treatment for the condition has been authorized for marketing in the EU (or, if a method exists, the new product would be a significant benefit to those affected by the condition).

We have sought and received orphan drug designation for Libmeldy and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-203 for MPS-IH from the FDA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our other product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not mean that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or EMA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the EU. The exclusivity period in the EU can be reduced to six years if a product no longer meets the criteria for orphan designation, including if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

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

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

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

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

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

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

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

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

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

Libmeldy and any of our product candidates for which we obtain regulatory approval will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. For example, as a post-marketing commitment, we are continuing to follow patients in the OTL-200 clinical development program for up to 15 years, and data will be presented to regulators at agreed points in order to further characterize the long-term efficacy and safety of Libmeldy.

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

In the EU, the advertising and promotion of our products are subject to EU laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising for medicinal products are consistent with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the marketing authorization granted for the medicinal product. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the EU. The applicable laws at EU level and in the individual EU Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and

imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance cGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory authority may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of the EMA and other regulatory authorities, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

Both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. This includes compliance with cGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third-party manufacturers would be required to ensure that all of our processes, quality systems, methods, and equipment are compliant with cGMP. Failure by us or by any of our third-party partners, including suppliers, manufacturers, and distributors to comply with EU laws and the related national laws of individual EU Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after the grant of a marketing authorization, and marketing of such products following the grant of an authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

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

Risks related to manufacturing and supply

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

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

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

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

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

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

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

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

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

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

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

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

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

We may be delayed or unable to identify, engage, successfully coordinate or qualify with treatment centers in the regions we are targeting as part of our commercial strategy, which could delay or prevent patients from receiving gene therapy treatments, if approved. If our treatment centers fail to perform satisfactorily, we may suffer reputational, operational, and business harm.

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

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

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

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

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

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

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

Our viral vectors and drug products are manufactured using technically complex processes in specialized facilities, sometimes using specialized equipment with highly specific raw materials and other production constraints. The complexity of these processes, as well as strict government standards for the manufacture and storage of our gene therapies, subjects us to manufacturing risks. While viral vectors and drug product released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following their release. In addition, process deviations or unanticipated effects of approved process changes may result in viral vector or drug product not complying with stability requirements or specifications. Our viral vectors and drug product must be stored and transported at temperatures within a certain range. If these environmental conditions deviate, our viral vectors and drug products' remaining shelf-lives could be impaired or their efficacy and safety could be negatively impacted, making them no longer suitable for use. For example, patients' cellular material must be received by the manufacturing facility typically within three days after collection, and our gene therapy must be received by the clinical site typically within ten days after shipping from the manufacturing facility. The occurrence, or suspected occurrence, of manufacturing and distribution difficulties can lead to lost inventories and, in some cases, product recalls, with consequential reputational damage and the risk of product liability. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product launches. Any interruption in the supply of finished products, due to transportation or other delays, including delays or disruptions resulting from the impact of the COVID-19 pandemic, or the loss thereof could hinder our ability to timely distribute our products and satisfy customer demand. Any unforeseen failure in the storage of the viral vectors or drug products or loss in supply could delay our clinical trials and result in a loss of our market share for our commercial products or our product candidates, if approved, and negatively affect our business, financial condition, results of operations and prospects.

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

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

Risks related to our reliance on third parties

We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialize product candidates. These collaborations may not be successful.

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

There could also be disagreements as to whether certain amounts are payable under our licensing and collaboration agreements. For example, there could be disputes as to whether certain milestone payments have been triggered. Such disputes would divert management attention, could harm our relationship with our collaborators or licensors, and could lead to payments that we do not currently anticipate.

We also entered into a collaboration with Pharming Group N.V., or Pharming, pursuant to which Pharming was granted worldwide rights to OTL-105, an investigational ex vivo autologous hematopoietic stem cell gene therapy for the treatment of hereditary angioedema. The Company will lead the completion of IND-enabling activities and oversee manufacturing of OTL-105 during pre-clinical and clinical development, which will be funded by Pharming.

We may enter into additional collaborations in the future. We have limited control over the amount and timing of resources that our current and future collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend on our and our collaborators' abilities to successfully perform the functions assigned to

each of us in these arrangements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator is responsible could be harmful to the public perception and prospects of our gene therapy platform.

Any collaborations we enter into in the future may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- we may not achieve any milestones, or receive any payments, under our collaborations, including milestones or payments that we expect to achieve or receive;
- the clinical trials conducted as part of these collaborations may not be successful;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our shareholders about the status of such product candidates;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates developed in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under such collaborations. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected.

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing shareholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation

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

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

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

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

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

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

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

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

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

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our pre-clinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing pre-clinical and clinical programs. While we will have agreements governing the activities of our academic partners and CROs, we will control only certain aspects of their activities and have limited influence over their actual performance.

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

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

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

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

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

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing CDMOs for our viral vectors and drug product, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials, including in some cases critical raw materials used in the manufacture thereof, must be manufactured in accordance with cGMP. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our viral vectors or product candidates that may not be detectable in final product testing. We or our CDMOs must supply all necessary documentation in support of a BLA or MAA on a timely basis and must adhere to the FDA's and EMA's cGMP and other applicable regulations that are enforced through facilities

inspection programs. Some of our CDMOs have not produced a commercially approved product and have never been inspected by the FDA or other regulatory body. Our quality systems and the facilities and quality systems of some or all of our CDMOs must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our viral vector or drug product or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted.

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

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

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

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

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

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

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

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

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;

- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers;
- interruptions, shortages, delivery delays and potential discontinuation of supply as a result of the COVID-19 global pandemic, or any recurrence of the pandemic or future pandemics; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

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

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

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

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

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

Risks related to commercialization of our product candidates

If we are unable to either establish effective sales and marketing capabilities or enter into agreements with third parties for such services, we may be unable to generate product revenue.

We are working to successfully commercialize Libmeldy in Europe, and we intend to commercialize our product candidates, if approved, in the United States, Europe and other markets. Given the relative rarity of the indications that we are targeting, we are commercializing Libmeldy, and we currently intend to commercialize any product candidates that are approved directly with specialized teams. We currently have a limited marketing and sales team, and we must build and expand our commercial infrastructure and capabilities or make arrangements with third parties to provide those services. If we are unable to do so, we may be unable to generate sufficient revenue to sustain our business.

Regardless of whether we establish our own sales and marketing capabilities or enter into third-party arrangements, there are risks involved. On the one hand, recruiting and training a commercial organization is both expensive and time consuming, and we could face delays in any product launch. If a product launch is delayed or does not occur, we may be unable to recoup our investment if we cannot retain or reposition our sales and marketing personnel. There are several factors that could inhibit our efforts to commercialize Libmeldy and our product candidates, if approved, on our own. These include, but are not limited to:

- we may be unable to recruit, train and retain adequate numbers of effective sales and marketing personnel;

- our sales personnel may be unable to obtain access to physicians or may be unable to persuade adequate numbers of physicians to prescribe Libmeldy and any future products that we may develop;
- we may face changes or setbacks at treatment centers contracted for the administration of any approved treatments;
- adverse events could occur;
- we are unable to offer complementary treatments, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- we may experience unforeseen costs and expenses associated with creating an independent sales and marketing organization.

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

On the other hand, there are risks with entering into third party arrangements for the performance of sales, marketing and distribution services. These include, but are not limited to:

- our product revenue or the profitability to us from these revenue streams may be lower than if we were to perform these services ourselves;
- we may be unable to enter into suitable third-party arrangements or we may only be able to do so on unfavorable terms, particularly given that we face competition in any search for third-party assistance; and
- we will likely have limited control over third parties, and they may fail to devote the necessary resources and attention to market and sell our products or product candidates, if approved, effectively.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may be unable to generate product revenue.

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

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

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

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

develop and commercialize products that are safer, more effective, have fewer or less severe side effects, have broader market acceptance, are more convenient or are less expensive than any product candidate that we may develop.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

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

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

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

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

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

Even if a product candidate displays a favorable efficacy and safety profile in pre-clinical studies and clinical trials, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our efforts to educate the medical

community and payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

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

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

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

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

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

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

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

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

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

Risks related to our business operations

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

Gene therapy remains a novel technology with only a limited number of gene therapy products approved to date. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. Adverse events in other lentiviral gene therapy trials unrelated to our product candidates could negatively impact our business. Our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates (such as the many adverse events that typically arise from the conditioning process), or adverse events in other lentiviral gene therapy trials, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

Increasing demand for compassionate use of our unapproved therapies could result in losses.

We are developing our autologous *ex vivo* gene therapies to address rare diseases for which there are currently limited or no available therapeutic options. Media attention to individual patients' expanded access requests has resulted in the introduction and passage of legislation at the local and national level referred to as "Right to Try" laws, which are intended to help enable patient access to unapproved therapies. Such legislation includes the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, which was signed into law in May 2018. New and emerging legislation regarding expanded access to unapproved drugs for life-threatening illnesses could negatively impact our business in the future.

A possible consequence of both activism and legislation in this area is the need for us to initiate an unanticipated expanded access program or to make our product candidates more widely available sooner than anticipated. We have limited resources and unanticipated trials or access programs could result in diversion of resources from our primary goals.

In addition, patients who receive access to unapproved drugs through compassionate use or expanded access programs have life-threatening illnesses and have exhausted all other available therapies. The risk for SAEs in this patient population is high, which could have a negative impact on the safety profile of our product candidates. This could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

We may be unable to effectively manage our programs.

In some instances, we may decide to discontinue our investment in programs after we've invested time and capital into such programs. For example, in May 2020, we announced a reduction of the investment in and scope of OTL-101 for ADA-SCID and OTL-300 for

TDT, and we have since returned licenses for both programs to the licensor. Additionally, in March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis, OTL-103 for treatment of WAS and OTL-102 for treatment of X-CGD. We may in the future decide to discontinue additional programs, and we may incur transition and termination costs. In addition, we may in the future decide to expand our operations to different territories and indications, including through in-licenses. Managing these expanded operations will pose challenges for us, and we cannot assure that we will be successful.

We face potential product liability.

The use of our product candidates in clinical trials and the sale of Strimvelis and Libmeldy or any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

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

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

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

An information security incident, including a cybersecurity breach, could have a negative impact to the Company's business or reputation.

Security incidents have become more prevalent across industries and may occur on our systems or on the systems of our third-party service providers. These security incidents may be caused by, or result in, security breaches, computer malware or malicious software, ransomware, computer hacking, denial of service attacks, security system control failures in our own systems or from service providers we use, email phishing, software vulnerabilities, social engineering, sabotage, drive-by downloads and the malfeasance of our or our service providers' employees, among other things. We have taken measures to detect, remediate and prevent future attacks and security threats. However, we may be affected, particularly given that such attacks are increasing in volume and sophistication and attack techniques frequently change.

Despite our security measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to, among other things, damage from computer viruses, unauthorized access, ransomware, natural disasters, terrorism, war and telecommunication and electrical failures. Furthermore, the COVID-19 pandemic and the related disruptions to our business and our collaborators', contractors' and consultants' businesses may increase the risk of security incidents. If any cyberattack or data breach were to occur in the future and cause interruptions in our or our collaborators', contractors' or consultants' operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data

from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or the inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

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

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

Recruiting and retaining qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. Competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in pre-clinical or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or the loss of the services of any key employee or advisor could harm our business.

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

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

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

Successful commercialization of our products depends, in part, on the availability of reimbursement for such products in the markets where we sell our products. Governmental health authorities, private health insurers and other organizations are focused on controlling healthcare costs, and these methods are not always specifically adapted for new technologies, such as gene therapy and therapies addressing rare diseases. Legislative and regulatory action affecting reimbursement could impact our ability to sell our products profitably.

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

- the demand for our products, if approved;
- our ability to set a sufficient price;

- our ability to generate revenue and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

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

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

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

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

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

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

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

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

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

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

- Additionally, a new California ballot initiative, the California Privacy Rights Act, or "CPRA," was passed in November 2020. The CPRA imposes additional obligations on companies covered by the legislation and will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. The effects of the CCPA and the CPRA are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement or litigation.
- Certain other state laws impose similar privacy obligations, and we also expect anticipate that more states to may enact legislation similar to the CCPA, which provides consumers with new privacy rights and increases the privacy and security obligations of entities handling certain personal information of such consumers. The CCPA has prompted a number of proposals for new federal and state-level privacy legislation. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs or changes in business practices and policies.
- Following the UK's withdrawal from the EU, the EU GDPR was incorporated into UK domestic law. UK-based organizations doing business in the EU will need to continue to comply with the EU GDPR and now also the UK GDPR. The UK is now regarded as a third country under the EU GDPR, but the European Commission has issued a decision recognizing the UK as providing adequate protection under the EU GDPR ("Adequacy Decision"). Therefore, transfers of personal data originating in the EU to the UK remain unrestricted. The UK Government has also confirmed that transfers of personal data originating in the UK to the EU may continue to flow freely. The UK Government has also now introduced a Data Protection and Digital Information Bill ("UK Bill") into the UK legislative process. The aim of the UK Bill is to reform the UK's data protection regime following Brexit. If passed, the final version of the UK Bill may have the effect of further altering the similarities between the UK and EEA data protection regime and threaten the UK Adequacy Decision from the EU Commission. This may lead to additional compliance costs and could increase our overall risk. The respective provisions and enforcement of the EU GDPR and UK GDPR may further diverge in the future and create additional regulatory challenges and uncertainties.

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

In the event we decide to conduct additional clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer or other processing of personal data regarding individuals in the EEA or the UK, including personal health data, is subject to the GDPR. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, where required obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, where required providing notification of data breaches, and taking certain measures when engaging third-party processors, including concluding data processing agreements, where required appointing data protection officers, where required conducting data protection impact assessments, and record-keeping. The GDPR also imposes strict rules and restrictions on the transfer of personal data to countries outside the EEA or the UK, including the United States (see below), and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20.0 million (£17.5 million) or 4% of annual global revenue, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. The GDPR may increase our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Compliance with the GDPR will be a rigorous and time-intensive

process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities.

Significantly, adequate safeguards must be implemented to enable the transfer of personal data outside of the EEA or the UK, in particular to the United States, in compliance with the GDPR (for example, the European Commission approved Standard Contractual Clauses, or SCCs, and the UK International Data Transfer Agreement/Addendum ("UK IDTA"). When relying on the SCCs /UK IDTA for data transfers, we may also be required to carry out transfer impact assessments to assess whether the recipient is subject to local laws which allow public authority access to personal data. The international transfer obligations under the EEA and UK data protection regimes will require significant effort and cost and may result in us needing to make strategic considerations around where EEA and UK personal data is transferred and which service providers we can utilize for the processing of EEA and UK personal data.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge and may not comply under one or more of such laws, regulations or guidance. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive share options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

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

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

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

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

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

- economic weakness, including inflation, or political instability in the United Kingdom and other non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;

- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the eligible members of the UK electorate for the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws or practice;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, 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 of our product candidates or relating to one or more of our product candidates. If these patent rights were enforced against us, we believe that we have defenses against any such action, including that these patents would not be infringed by our product candidates or that these patents are not valid. However, if these patents were enforced against us and defenses to such enforcement were unsuccessful, unless we obtain a license to these patents, which may not be available on commercially reasonable terms, or at all, we could be liable for damages and precluded from commercializing any products and product candidates that were ultimately held to infringe these patents, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

We are highly dependent on the intellectual property and data licensed to us by third parties, including technology related to the manufacture and use of our products and product candidates. We have in-licensed certain know-how and data from GSK and Telethon-OSR relating to Libmeldy, certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-IH, and certain other intellectual property for our clinical and pre-clinical programs. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

Our in-licensed intellectual property is often limited to particular fields and is often subject to certain retained rights. We may not have the rights to use in-licensed intellectual property, data or know-how from one program in another program. As a result, we may not be free to commercialize certain of our products or product candidates in fields or territories of interest to us. Furthermore, if the licenses are not exclusive in territories of interest to us, we may be unable to prevent competitors from developing and commercializing competitive products in territories included in our licenses. Licenses (including sublicenses) to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business.

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

eliminated and our right to develop and commercialize any of our products and product candidates that are the subject of such licensed rights could be adversely affected.

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

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

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

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

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

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

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

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

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

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

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

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

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

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

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

In the future, if we obtain an issued patent covering one of our present or future product candidates, depending upon the timing, duration and specifics of any FDA marketing approval of such product candidates, such patent may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. A patent may only be extended once and only based on a single approved product. However, we may not be granted an extension because of, for example, failure to obtain a granted patent before approval of a product candidate, failure to exercise due diligence during the testing phase or regulatory review process, failure to apply within applicable deadlines, failure to apply prior to expiration of relevant patents or otherwise our failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In addition, we do not control the efforts of our licensors to obtain a patent term extension, and there can be no assurance that they will pursue or obtain such extensions to patents that we may license from them.

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

Some of the intellectual property rights we have licensed may have been generated through the use of U.S. government and state funding and may therefore be subject to certain federal and state laws and regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future products and product candidates pursuant to the Bayh-Dole Act of 1980. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government -funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. With respect to state funding, specifically funding via the California Institute of Regenerative Medicine, or CIRM, the grantee has certain obligations and the state or CIRM has certain rights. For example, the grantee has an obligation to share intellectual property, including research results, generated by CIRM-funded research, for research use in California.

Intellectual property rights and regulatory exclusivity rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and they may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- the patents of others may have an adverse effect on our business;

- others, including one or more of our competitors, may reverse engineer or independently develop the know-how or data, including clinical data, that we rely on for a competitive advantage;
- others may be able to make gene therapy products that are similar to our products or product candidates but that are not covered by the claims of the patents that we license or may own or license in the future or by our other intellectual property rights;
- we, our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patents or pending patent applications that we license or may own or license in the future;
- we, our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own or license in the future will not lead to issued patents;
- issued patents that we hold rights to or may hold rights to in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- one or more of our products or product candidates may never be protected by patents;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- we or our licensors or collaborators may choose not to file a patent application for certain trade secrets or know-how, and a third party may subsequently file a patent application or obtain a patent covering such intellectual property.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

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

Competitors may infringe, misappropriate or otherwise violate patents, trademarks, copyrights or other intellectual property that we own or in-license. To counter infringement, misappropriation or other unauthorized use, we may be required to file claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived violators could provoke these parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their intellectual property, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any future patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition.

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

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

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

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

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own or such assignments may not be self-executing or may be breached. Our licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of employees, consultants or others who are involved in developing our products or product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

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

Changes in either the patent laws or the interpretation of the patent laws in the United States or other jurisdictions could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents.

The patent positions of companies engaged in the development and commercialization of biologics are particularly uncertain. Two cases involving diagnostic method claims and "gene patents" have been decided by the Supreme Court. The Supreme Court issued a decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, or *Prometheus*, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as "administering" or "determining" steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. Thereafter, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. Subsequently, the Supreme Court issued its decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, or *Myriad*, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. *Myriad* held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent-eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible. Thereafter, the USPTO issued a guidance memorandum instructing USPTO examiners on the ramifications of the *Prometheus* and *Myriad* rulings and apply the *Myriad* ruling to natural products and principles including all naturally occurring nucleic acids.
Certain claims of our in-licensed patent applications contain, and any future patents we may obtain may contain, claims that relate to specific recombinant DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties.

We cannot assure that our efforts to seek patent protection for one or more of our products and product candidates will not be negatively impacted by the decisions described above, rulings in other cases, or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court's decisions in *Prometheus* and *Myriad* may have on the ability of life science companies to obtain or enforce patents relating to their products in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent rights and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court held in *Myriad* that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we

may deem it necessary to defend ourselves against these claims by asserting non-infringement or invalidity positions or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter, the result of which could have a material adverse effect on our business.

Risks related to ownership of our securities

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

The trading price of our ADSs has fluctuated and may continue to fluctuate significantly. The market price of our ADSs depends on a number of factors, some of which are beyond our control. For example, the trading price of our ADSs may be affected by:

- adverse results or delays in pre-clinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by our current or future collaborators to successfully develop and commercialize product candidates for which we are eligible to receive milestone and royalty payments;
- failure by us to adequately scale our manufacturing capabilities and commercial and sales organization to succeed in our commercialization efforts of Libmeldy;
- failure by us to succeed in our ongoing commercialization of Strimvelis;
- failure by us to gain broad insurance coverage and reimbursement for our product candidates, if approved;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial or other projections we may provide to the public;
- failure by us to meet or exceed the financial or other projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- general economic, geopolitical and market conditions, including the significant disruptions to the U.S. and global economies and the related significant volatility and negative pressure in financial markets caused by the COVID-19 global pandemic, supply chain issues, inflationary pressures and the ongoing conflict in the Ukraine;
- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

In addition, companies trading in the stock market in general, and the Nasdaq Capital Market and in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these

companies. Broad market and industry factors may negatively affect the market price of our ADSs, regardless of our actual operating performance.

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

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

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

Based upon our ordinary shares outstanding as of May 9, 2023, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 62.8% of our ordinary shares and ADSs. In computing the number of ordinary shares beneficially owned by a person, ordinary shares subject to options, or other rights held by such person that are currently exercisable or will become exercisable within 60 days of May 9, 2023, are considered outstanding. These ordinary shares, however, are not included in the number of shares outstanding as of May 9, 2023. (In other words, in calculating the beneficial ownership percentage, there are ordinary shares in the numerator that are not reflected in the denominator.) Depending on the level of attendance at our meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, and the approval of certain significant corporate transactions. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that our shareholders may believe are in their best interest as shareholders. Some of these persons or entities may have interests that are different than those of our other shareholders. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs were sold in our initial public offering and have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

Future sales, or the possibility of future sales, of a substantial number of our securities could adversely affect the price of the shares and dilute shareholders.

Additional sales of our ADSs, or the perception that these sales could occur, could cause the market price of our ADSs to decline. If any of our large shareholders or members of our management team sell substantial amounts of ADSs in the public market, or the market perceives that such sales may occur, the market price of our ADSs and our ability to raise capital through an issue of equity securities in the future could be adversely affected. Additionally, we filed a registration statement with the SEC and may issue securities in one or more underwritten transactions, in “at-the-market” offerings or in other transactions from time to time. If we were to issue such securities in the public market, the trading price of our ADSs could decline.

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

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

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

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

when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to ADSs or to the withdrawal of ordinary shares or other deposited securities.

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

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

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

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

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

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

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

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

Except as described in the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the depositary to vote the ordinary shares underlying their ADSs. Otherwise, holders of ADSs will not be able to exercise their right to vote unless they withdraw the ordinary shares underlying their ADSs to vote them in person or by proxy in accordance with applicable laws and regulations and our Articles of Association. Even so, ADS holders may not know about a meeting far enough in advance to withdraw those ordinary shares. If we ask for the instructions of holders of the ADSs, the depositary, upon timely notice from us, will notify ADS holders of the upcoming vote and arrange to deliver our voting materials to them. Upon our request, the depositary will mail to holders a shareholder meeting notice that contains, among other things, a statement as to the manner in which voting instructions may be given. We cannot guarantee that ADS holders will receive the voting materials in time to ensure that they can instruct the depositary to vote the ordinary shares underlying their ADSs. A shareholder is only entitled to participate in, and vote at, the meeting

of shareholders, provided that it holds our ordinary shares as of the record date set for such meeting and otherwise complies with our Articles of Association. In addition, the depositary's liability to ADS holders for failing to execute voting instructions or for the manner of executing voting instructions is limited by the deposit agreement. As a result, holders of ADSs may not be able to exercise their right to give voting instructions or to vote in person or by proxy and they may not have any recourse against the depositary or us if their ordinary shares are not voted as they have requested or if their shares cannot be voted.

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

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

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

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

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

Sales of a substantial number of our ADS in the public market, or the perception that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. As of March 31, 2023, we had outstanding 184,256,359 voting and non-voting shares. The holders of 8,611,375 shares of our ordinary shares are entitled to rights with respect to the registration of their ordinary shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these ordinary shares under the Securities Act would result in the ADSs representing them becoming freely tradable without restriction, except for ADSs purchased by affiliates. In addition, our directors, executive officers and other affiliates may establish, and certain executive officers, directors and affiliates have established, programmatic selling plans under Rule 10b5-1 of the Exchange Act, for the purpose of effecting sales of our ADSs. Generally, sales under such plans by our executive officers and directors require public filings. Any sales of securities by these shareholders, or the perception that those sales may occur, under such programmed selling plans, could have a material adverse effect on the trading price of our ADSs. In addition, as of March 31, 2023, 22,933,973 ordinary shares reserved for issuance upon the exercise of existing options outstanding and issuance of performance-based and time-based restricted shares under our current equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

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

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

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting and, once we are no longer a "smaller reporting company", we will be required to furnish an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In order to achieve and maintain compliance with Section 404, we have documented and evaluated our internal control over financial reporting, which is both costly and challenging. In this regard, we continue to dedicate internal resources, have engaged outside consultants and adopted a detailed work plan to continually assess and document the adequacy of internal control over financial reporting, taken steps to improve control processes as appropriate, validated through testing that controls are functioning as documented and have

implemented a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk in any given year that we will not be able to conclude within the prescribed time frame that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. Moreover, if in the future we are required to obtain an opinion as to the effectiveness of our internal control over financial reporting and if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our ADSs could be negatively affected, and we could become subject to investigations by the SEC or other regulatory authorities or to shareholder litigation, which could have an adverse impact on the market price or our ADSs and cause us to incur additional expenses.

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

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

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

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

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

The principal differences include the following:

- Under English law and our Articles of Association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings.
- Under English law, it is only on a poll that the number of shares determines the number of votes a holder may cast. The voting rights of ADSs are also governed by the provisions of a deposit agreement with our depositary bank.
- Under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise.
- Under English law and our Articles of Association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the Articles of Association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve certain significant transactions.
- In the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, a bidder seeking to acquire us by means of a takeover offer would need to make an offer for all of our outstanding ordinary shares/ADSs. If acceptances are not received for 90% or more of the ordinary shares/ADSs under the offer, under English law, the bidder cannot complete a “squeeze out” to obtain 100% control of us. Accordingly, acceptances of 90% of our outstanding ordinary shares/ADSs will likely be a condition in any takeover offer to acquire us, not 50% as is more common in tender offers for corporations organized under Delaware law. By contrast, a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting for approval.
- Under English law and our Articles of Association, shareholders and other persons whom we know or have reasonable cause to believe are, or have been, interested in our shares may be required to disclose information regarding their interests in our shares upon our request, and the failure to provide the required information could result in the loss or restriction of rights attaching to the shares, including prohibitions on certain transfers of the shares, withholding of dividends and loss of voting rights. Comparable provisions generally do not exist under U.S. law.

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

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

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

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

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Risks related to taxation

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

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

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

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

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

Our transfer pricing arrangements are not generally binding on applicable tax authorities. The price charged for products, services, or the royalty rates and other amounts paid for intellectual property rights, could be challenged by the various tax authorities, resulting in additional tax liability, interest or penalties. There can be no assurance that a taxing authority will not have a different interpretation of

applicable law and assess us with additional taxes. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a ‘‘permanent establishment’’ under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. If we are assessed with additional taxes, this may result in a material adverse effect on our results of operations and financial condition.

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

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

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

We believe that we were not a CFC in the 2022 taxable year, but we may become a CFC in a subsequent taxable year. If we are classified as both a CFC and a passive foreign investment company, or PFIC (as discussed below), we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

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

Under the Code, we will be a PFIC, for any taxable year in which (i) 75% or more of our gross income consists of passive income or (ii) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For the purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. holder holds our ordinary shares or ADSs, the U.S. holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

Based on the current and expected composition of our income and assets and the value of our assets, we believe that we were a PFIC for U.S. federal income tax purposes for our taxable year ended December 31, 2022. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income, which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by the spending of the cash we raise in any offering.

In certain circumstances, a U.S. holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a “qualified electing fund,” or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute “marketable” securities under the Code), which each require the inclusion of a pro rata share of our income on a current basis. Because it was possible we were a PFIC for the 2022 taxable year, we currently expect that we will provide the information necessary for U.S. holders to make a QEF Election. We may elect to provide such information on our website (www.ORTX.com). A U.S. holder would

also be able to make a mark-to-market election with respect to our ordinary shares or ADSs as long as those shares or ADSs constitute marketable securities under the Code.

We may be unable to use UK net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable UK tax legislation.

As a UK incorporated and tax resident entity, we are subject to UK corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any UK corporation tax. As of December 31, 2022, we had cumulative carryforward tax losses of $633.4 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to UK profits incurred on or after April 1, 2017, will be limited each year to £5.0 million plus, broadly, an incremental 50% of UK taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a company that carries out extensive research and development activities, we seek to benefit from two UK research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are currently eligible for inclusion within these tax credit cash rebate claims.

In the future we will continue to seek to benefit from these programs; however, the United Kingdom Government's Autumn Statement on November 17, 2022, announced reductions in the level of credits offered under the SME Program that will take effect from April 2023, along with other changes outlined further below. Under the SME Program, we are currently in principle able to surrender some of our trading losses that arise from our qualifying research and development activities for a cash rebate of up to 33.35% of such qualifying research and development expenditures. The majority of our research, clinical trials management and manufacturing development activities are currently eligible for inclusion within these tax credit cash rebate claims. The cash rebate available from April 2023 is expected to reduce to up to 18.6% of qualifying research and development expenditures, which (if we continue to qualify as a SME) would represent a significant reduction in cash receivable from the United Kingdom Government. Furthermore, we may not be able to continue to claim payable research and development tax credits in the future if we cease to qualify as a SME, based on size criteria concerning employee headcount, turnover and gross assets. There is also a cap on payable credit claims under the SME Program in excess of £20,000 by reference to, broadly, three times the total PAYE and NICs liability of the company, subject to an exception which prevents the cap from applying. That exception requires the company to be creating, taking steps to create, or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties which does not exceed 15% of the total claimed. If such an exception does not apply, this could restrict the amount of payable credit that we claim. If we cease to be eligible for the SME Program, we may be able to claim alternative credits under the RDEC Program (in addition to credits that we currently claim under that Program). The RDEC Program does not entitle us to cash rebates in the same way as the SME Program, but instead (broadly) functions as a taxable credit against United Kingdom corporation tax (although the credit may be repayable to a loss-making company in certain circumstances). The United Kingdom Government has announced an increase to the rate of the RDEC credit from 13% to 20% from April 2023 (although the RDEC Program on the whole is less advantageous than the SME Program).

Additional changes to the R&D tax relief legislation, expected to take effect from April 2023, introduce restrictions on relief that may be claimed for expenditure on sub-contracted R&D activity, broadly requiring either that workers carrying on such activity are subject to UK PAYE or, where work is undertaken outside the UK, that this must be due to geographical, environmental or social conditions not replicable in the UK. These restrictions may impact the quantum of R&D relief that we are able to claim in the future. In addition, the UK government is currently consulting on the potential replacement of the SME Program and RDEC Program with a single program, operating similarly to the RDEC Program, which may, inter alia, change the present treatment of sub-contracted R&D work and introduce different thresholds and caps on expenditure and relief. If enacted, the new program would be expected to have an effect for expenditure incurred from April 2024 onward and could have a material impact on the quantum of R&D relief that we are eligible to claim.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenue from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenue and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the UK research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and

certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

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

Under Section 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership by certain stockholders over a three-year period, the corporation's ability to use its pre-change tax attributes (such as research and development tax credits) to offset its post-change tax liabilities may be limited. We have completed several financings since our inception, which we believe have resulted in an ownership change as defined by Section 382 of the Code. We may also experience ownership changes in the future as a result of subsequent shifts in our share ownership. As a result, if we incur U.S. federal tax liability, our ability to use our pre-change tax attributes to offset U.S. federal tax liability may be subject to limitations, which could potentially result in increased future tax liability to us.

Risks related to our Domicile

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

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

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

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

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

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

General Risk Factors

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

We currently have $30.1 million of principal indebtedness outstanding under our senior term facilities agreement, or the amended Credit Facility, with MidCap Financial (Ireland) Limited. Our existing indebtedness and any additional indebtedness we may incur could require us to divert funds identified for other purposes for debt service and impair our liquidity position.

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

- increasing our vulnerability to general adverse economic and industry conditions or increased interest rates;
- restricting our ability to use our cash, cash equivalents and marketable securities for other purposes;
- limiting our flexibility in planning for or reacting to changes in our business and the markets in which we operate, which would place us at a competitive disadvantage compared to our competitors that may have less debt;
- limiting our ability to borrow additional funds for working capital, capital expenditures and other investments; and
- failing to comply with the covenants in our debt agreements could result in all of our indebtedness becoming immediately due and payable.

If our business does not generate sufficient cash flow from operations or if future borrowings are not available to us under the Amended Credit Facility or otherwise in amounts sufficient to enable us to fund our liquidity needs, our financial condition and results of operations may be adversely affected. Our inability to make scheduled payments on our debt obligations in the future would require us to refinance all or a portion of our indebtedness on or before maturity, sell assets or seek additional equity investment. We may not be able to take any of such actions on a timely basis on terms satisfactory to us or at all.

The Amended Credit Facility contains customary restrictive covenants relating to the operation of our business, including restrictions on our ability to:

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

Such restrictions could affect our ability to take certain actions from time to time.

We may be adversely affected by natural disasters, and our business continuity and disaster recovery plans may not adequately protect us.

Natural disasters, including earthquakes, fires, flooding, and health epidemics and pandemics, among other things, could severely disrupt our business. If a natural disaster occurs, we may be unable to use all or a significant portion of our facilities, which could make it difficult or impossible for us to continue our business or a portion of our business for a substantial period of time. A natural disaster could also damage critical infrastructure and affect our third-party contract manufacturers. Our disaster recovery and business continuity plans are currently limited and may not prove adequate in the event of a serious natural disaster or similar event. As such, we could incur substantial expenses if a natural disaster occurs, which could have a material impact on our business.

Our business may be affected by public health crises, including the COVID-19 pandemic.

Public health crises such as pandemics or similar outbreaks can adversely impact our business. For example, the COVID-19 global pandemic caused significant disruptions to the U.S. and global economies, contributed to volatility in the financial markets, and led to measures that impacted various aspects of our business, including our clinical and regulatory efforts as well as our supply chain. Renewed outbreaks, including different variants of the virus, could negatively impact our business operations.

In addition, in response to the COVID-19 pandemic, we implemented a hybrid work policy for many employees, whereby eligible employees spend only part of their time working in the office. Remote working creates risks to our business, including increased cybersecurity risks. We may also experience difficulty in recruiting and onboarding new employees as a result of remote working.

The extent to which pandemics, including the COVID-19 pandemic, may impact our business, and our clinical development and regulatory efforts, as well as our supply chain, will depend on future developments that are highly uncertain and cannot be predicted with confidence, such as the geographic spread of a disease, the duration of the outbreak, government actions, such as travel restrictions, quarantines and social distancing requirements in the U.S. and in other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and in other countries to contain and treat the disease. Accordingly, we cannot predict the impact of pandemics, including the COVID-19 pandemic, with any certainty. However, these effects could materially and

adversely affect our business, financial condition, results of operations and growth prospects, which may in turn also have the effect of heightening many of the other risks and uncertainties described elsewhere in this “Risk Factors” section.

Any changes to existing accounting pronouncements or taxation rules or practices may cause adverse fluctuations in our reported results of operations or affect how we conduct our business.

A change in accounting pronouncements or taxation rules or practices could have a significant effect on our reported results and may affect our reporting of transactions completed before the change is effective. New accounting pronouncements, taxation rules and varying interpretations of accounting pronouncements or taxation rules have occurred in the past and may occur in the future. We could be required to modify a current tax or accounting position as a result of any such change, and this could adversely affect our reported financial results and could change the way we conduct our business.

We could be subject to securities class action litigation.

We could be the subject of a securities class action litigation. The risk is especially relevant to us because such litigation is often brought against companies following a decline in the market price of their securities, and biotechnology and pharmaceutical companies have experienced significant securities price volatility in recent years. If such a litigation were brought against us, it could result in substantial costs and could divert management’s attention and resources, which would be harmful to our business.

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

During the quarter ended March 31, 2023, we did not have any sales of unregistered securities except as detailed on the Company's Current Report on Form 8-K, filed March 6, 2023.

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
4.1	Form of Warrant (as filed as Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed on March 6, 2023 and incorporated herein by reference).
10.1**	Securities Purchase Agreement, dated March 6, 2023, 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 March 6, 2023 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)

* Filed herewith

# Indicates a management contract or any compensatory plan, contract or arrangement.

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

**Schedules and exhibits have been omitted pursuant to Item 601(a)(5) of Regulation S-K. A copy of any omitted schedule and/or exhibit will be furnished to the SEC upon request.

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 15, 2023

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: May 15, 2023

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 on Form 10-Q 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 15, 2023

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal 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 on Form 10-Q 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 15, 2023

By: /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer
(Principal Financial Officer and Principal Accounting 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, 2023, 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 results of operations of the Company.

Date: May 15, 2023

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: May 15, 2023

By: /s/ Frank E. Thomas

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