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 June 30, 2020

OR

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

For the transition period from to

Commission File Number: 001-38722

ORCHARD THERAPEUTICS PLC
(Exact Name of Registrant as Specified in its Charter)

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

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

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

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

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

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

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

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

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

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

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

As of July 31, 2020, the registrant had 97,577,100 ordinary shares, nominal value £0.10 per share, outstanding.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Quarterly Report on Form 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 Quarterly Report on Form 10-Q are based upon information available to our management as of the date of this Quarterly Report on Form 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 Quarterly Report on Form 10-Q include, but are not limited to, statements about:

- the timing, progress and results of clinical trials and preclinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the timing, scope or likelihood of regulatory submissions, filings, and approvals;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the market opportunity for and size of the patient populations for our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial product, product candidates and technology, including the execution of recent revisions to our vision and growth strategy;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our commercial product and product candidates, if approved;
- the adequacy, scalability and commercial viability of our manufacturing capacity, methods and processes, including those of our manufacturing partners, and plans for future development;
- the rate and degree of market acceptance and clinical utility of our commercial product and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- the impact of the COVID-19 global pandemic and related downturn of the U.S. and global economies, as well as on our business operations, including clinical trials, and the operations of our third-party manufacturers and suppliers;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our commercial product and product candidates;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing; the impact of laws and regulations;
- our ability to attract and retain qualified employees and key personnel;
- our ability to raise capital, particularly in light of the impact of the COVID-19 global pandemic and the related impact on the US and global economies;
- our ability to contract with third party suppliers and manufacturers and their ability to perform adequately;
- the expected cost savings resulting from our recently announced changes to our strategic vision;
- our projected financial performance and 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;
- our cash runway into 2022; and
- our risks and uncertainties, including those listed under the caption "Item 1A. Risk Factors."

You should refer to the section titled "Item 1A. Risk Factors" for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot be assured that the forward-looking statements in this Quarterly Report on Form 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 Quarterly Report on Form 10-Q and the documents that we reference in this Quarterly Report on Form 10-Q and have filed as exhibits to this Quarterly Report on Form 10-Q completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

PART I—FINANCIAL INFORMATION

Item 1. Financial Statements.

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

	June 30, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 41,174	$ 19,053
Marketable securities	187,480	305,937
Trade receivables	723	1,442
Prepaid expenses and other current assets	12,760	8,530
Research and development tax credit receivable, current	12,995	14,934
Total current assets	255,132	349,896
Non-current assets:		
Operating lease right-of-use-assets	18,642	19,415
Property and equipment, net	5,460	7,596
Research and development tax credit receivable	19,734	13,710
Restricted cash	4,266	4,264
Other assets	11,342	4,400
Total assets	$ 314,576	$ 399,281
Liabilities and shareholders’ equity		
Current liabilities:		
Accounts payable	$ 15,590	$ 11,984
Accrued expenses and other current liabilities	19,811	37,980
Operating lease liabilities	5,924	5,892
Notes payable, current	694	—
Total current liabilities	42,019	55,856
Notes payable, long-term	24,192	24,699
Operating lease liabilities, net of current portion	17,171	15,320
Other long-term liabilities	4,173	4,213
Total liabilities	87,555	100,088
Commitments and contingencies (see Note 11)		
Shareholders’ equity:		
Ordinary shares, £0.10 nominal value	12,405	12,331
Additional paid-in capital	757,296	738,481
Accumulated other comprehensive income	9,050	2,042
Accumulated deficit	(551,730)	(453,661)
Total shareholders’ equity	227,021	299,193
Total liabilities and shareholders’ equity	$ 314,576	$ 399,281

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 June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Product sales, net	$ 597	$ —	$ 597	$ —
Costs and operating expenses:				
Cost of product sales	191	—	191	—
Research and development	31,568	40,478	$ 56,404	57,971
Selling, general and administrative	15,659	13,674	35,804	24,464
Total costs and operating expenses	47,418	54,152	92,399	82,435
Loss from operations	(46,821)	(54,152)	(91,802)	(82,435)
Other income (expense):				
Interest income	892	1,727	2,372	3,350
Interest expense	(568)	(245)	(1,181)	(245)
Other income (expense), net	(943)	1,368	(7,733)	(2,118)
Total other income (expense), net	(619)	2,850	(6,542)	987
Net loss before income tax	(47,440)	(51,302)	(98,344)	(81,448)
Income tax (expense) benefit	(60)	772	275	179
Net loss attributable to ordinary shareholders	(47,500)	(50,530)	(98,069)	(81,269)
Other comprehensive income (loss)				
Foreign currency translation adjustment	610	(1,443)	6,643	1,608
Unrealized gain (loss) on marketable securities	1,385	108	364	108
Total other comprehensive income (loss)	1,995	(1,335)	7,007	1,716
Total comprehensive loss	$ (45,505)	$ (51,865)	$ (91,062)	$ (79,553)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (0.48)	$ (0.56)	$ (0.99)	$ (0.92)
Weighted average number of ordinary shares outstanding, basic and diluted	99,251,314	89,712,916	99,048,498	88,369,311

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

ORCHARD THERAPEUTICS PLC

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

	Six Months Ended June 30, 2020	Six Months Ended June 30, 2019
Cash flows from operating activities:		
Net loss attributable to ordinary shareholders	$ (98,069)	$ (81,269)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	1,081	775
Non-cash share-based compensation	15,558	8,451
Impairment of long-lived assets	5,650	—
Non-cash interest expense	254	46
Non-cash consideration for licenses	791	—
Amortization of Strimvelis loss provision	(2,018)	(2,589)
Amortization of premium (discount) on marketable securities	169	(232)
Other non-cash adjustments	6,984	2,860
Changes in operating assets and liabilities:		
Trade receivables	642	370
Research and development tax credit receivable	(5,989)	(9,913)
Prepaid expenses, other current assets and other assets	(3,313)	1,125
Operating leases, right-of-use assets	1,525	1,324
Accounts payable, accrued expenses and other current liabilities	(9,644)	6,802
Other long-term liabilities	—	(897)
Operating lease liabilities	(1,633)	30
Net cash used in operating activities	(88,012)	(73,117)
Cash flows from investing activities:		
Proceeds from sales and maturities of marketable securities	168,140	—
Purchases of marketable securities	(49,494)	(286,399)
Payment of construction deposit	(10,000)	—
Receipt of funds from construction deposit	1,876	—
Purchases of property and equipment	(2,484)	(589)
Net cash provided by (used in) investing activities	108,038	(286,988)
Cash flows from financing activities:		
Issuance of debt from credit facility, net of debt issuance costs paid	—	24,695
Proceeds from share options and ESPP shares	2,582	1,270
Issuance of ADSs in follow-on offering, net of offering costs paid	—	130,163
Net cash provided by financing activities	2,582	156,128
Effect of exchange rate changes on cash, cash equivalents, and restricted cash	(485)	922
Net increase (decrease) in cash, cash equivalents and restricted cash	22,123	(203,055)
Cash, cash equivalents, and restricted cash, beginning of period	23,317	339,681
Cash, cash equivalents, and restricted cash, end of period	$ 45,440	$ 136,626
Supplemental disclosure of non-cash investing and financing activities		
Deferred offering costs and debt issuance costs in accounts payable and accrued expenses	—	726
Property and equipment included in accounts payable and accrued expenses	125	262
Lease assets obtained in exchange for new operating lease liabilities	3,752	—
Shares issued as part of license agreement	791	—
Supplemental disclosure of cash flow information:		
Cash paid for taxes	1,321	—
Cash paid for interest	927	199

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements Shareholders' Equity

(In thousands, except share and per share amounts)

(unaudited)

	Ordinary Shares		Additional Paid-In Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total
	Shares	Amount				
Balance at December 31, 2018	85,865,557	$ 10,924	$ 587,490	$ 3,163	$ (290,239)	$ 311,338
Share-based compensation expense	—	—	3,821	—	—	3,821
Exercise of share options	1,471	—	4	—	—	4
Other comprehensive income	—	—	—	3,051	—	3,051
Net loss attributable to ordinary shareholders	—	—	—	—	(30,739)	(30,739)
Balance at March 31, 2019	85,867,028	$ 10,924	$ 591,315	$ 6,214	$ (320,978)	$ 287,475
Share-based compensation expense	-	-	4,630	—	—	4,630
Exercise of share options	532,889	69	504	—	—	573
Issuance of ESPP shares	60,335	8	685	—	—	693
Issuance of ADSs in follow-on offering, net of issuance costs of $620	9,725,268	1,233	128,418	—	—	129,651
Other comprehensive income	—	—	—	(1,335)	—	(1,335)
Net loss attributable to ordinary shareholders	—	—	—	-	(50,530)	(50,530)
Balance at June 30, 2019	96,185,520	$ 12,234	$ 725,552	$ 4,879	$ (371,508)	$ 371,157
Balance at December 31, 2019	96,923,729	$ 12,331	$ 738,481	$ 2,042	$ (453,661)	$ 299,193
Share-based compensation expense	—	—	9,479	—	—	9,479
Exercise of share options	230,836	30	1,408	—	—	1,438
Other comprehensive income	—	—	—	5,013	—	5,013
Net loss attributable to ordinary shareholders	—	—	—	—	(50,569)	(50,569)
Balance at March 31, 2020	97,154,565	$ 12,361	$ 749,368	$ 7,055	$ (504,230)	$ 264,554
Share-based compensation expense	—	—	6,079	—	—	6,079
Exercise of share options	214,299	27	643	—	—	670
Issuance of ESPP shares	53,462	7	425	—	—	432
Ordinary shares issued as part of license agreements	75,413	10	781	—	—	791
Other comprehensive income	—	—	—	1,995	—	1,995
Net loss attributable to ordinary shareholders	—	—	—	—	(47,500)	(47,500)
Balance at June 30, 2020	97,497,739	$ 12,405	$ 757,296	$ 9,050	$ (551,730)	$ 227,021

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

Notes to the Condensed Consolidated Financial Statements
(unaudited)

1. Nature of the Business

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

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

The Company is subject to risks and uncertainties common to development-stage companies in the biotechnology industry. There can be no assurance that the Company's research and development will be successfully initiated or 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 scientific and technological innovation and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and service providers. Even if the Company's product development efforts are successful in gaining regulatory approval, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

The Company is subject to risks associated with the COVID-19 pandemic. In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy where the Company operates, have placed significant restrictions on travel. While some COVID-19 restrictions have been relaxed, limitations on travel and other social distancing measures have had an effect on the Company's preclinical and clinical activities and regulatory timelines. Commercial activity associated with the Company's EMA-approved gene therapy for ADA-SCID, Strimvelis®, had been postponed by the treatment site but resumed in June 2020. Any prolonged material disruptions to the Company's employees, suppliers, contract manufacturers, vendors, patients, government sponsored funding programs or the Company's marketable securities could impact operating results and could lead to impairments. To date the Company has recorded impairments on long-lived assets that are due to a combination of a corporate restructuring and COVID-19 market impacts (see Note 8). The capital markets have experienced significant volatility as a result of the pandemic and the Company's ability to access the capital markets in the future could be impacted if disruptions in the capital markets continue.

Through June 30, 2020, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares and ADSs in the Company's initial public offering ("IPO") and a subsequent follow-on offering, as well as with certain grant and reimbursement payments and a drawdown on its credit facility, described in note 6 below. The Company has incurred recurring losses since its inception. As of June 30, 2020, the Company had an accumulated deficit of $551.7 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expects that its cash, cash equivalents, and marketable securities on hand as of June 30, 2020 of $228.7 million, will be sufficient to fund its operations and capital expenditure requirements through at least the next twelve months.

The Company will seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements, or any combination thereof. 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 and ADS holders. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

2. Basis of Presentation and Summary of Significant Accounting Policies

Basis of presentation

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

The accompanying unaudited condensed consolidated interim financial statements should be read in conjunction with the audited consolidated financial statements and accompanying notes included in the Company's Annual Report on Form 10-K filed with the SEC on February 27, 2020 (the "Annual Report"). The condensed consolidated balance sheet as of December 31, 2019 was derived from audited consolidated financial statements included in the Company's Annual Report but does not include all disclosures required by U.S. GAAP.

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

Use of estimates

The preparation of condensed consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the condensed consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these condensed consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the research and development tax credit receivable, share-based compensation, operating lease assets and liabilities, and income taxes. The full extent to which the COVID-19 pandemic will directly or indirectly impact the Company's business, results of operations and financial condition, including sales, expenses, reserves and allowances, manufacturing, clinical trials, research and development costs and employee-related costs, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and the actions taken to contain it or treat COVID-19, as well as the economic impact on local, regional, national and international customers and markets. The Company has made estimates of the impact of COVID-19 within the Company's financial statements and there may be changes to those estimates in future periods. As of the date of issuance of these unaudited condensed consolidated financial statements, the Company is not aware of any specific event or circumstance that would require the Company to update estimates, judgments or revise the carrying value of any assets or liabilities. Actual results may differ from these estimates.

Foreign currency

The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the parent company, Orchard Therapeutics plc, is the U.S. dollar because it predominantly raises finances and expends cash in U.S. dollars. The functional currency of the Company's subsidiary operations is the applicable local currency. Transactions in foreign currencies are translated into the functional currency of the subsidiary in which they occur at the foreign exchange rate in effect on the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are translated into the functional currency of the relevant subsidiary at the foreign exchange rate in effect on the balance sheet date. Non-monetary assets and liabilities denominated in foreign currencies that differ from the functional currency are translated into the functional currency at the exchange rates prevailing at the date of the transaction. The Company recorded realized and unrealized foreign currency transaction losses of $0.9 million and gains of $1.6 million for the three months ended June 30, 2020 and 2019, respectively. The Company recorded realized and unrealized foreign currency transaction losses of $7.4 million and $1.9 million for the six months ended June 30, 2020 and 2019, respectively. These amounts are included in other income (expense) in the condensed consolidated statements of operations and comprehensive loss.

The results of operations for subsidiaries, the functional currency of which is not the U.S. dollar, are translated at an average rate for the period in which this rate approximates to the foreign exchange rates ruling at the dates of the transactions and the balance sheets of these subsidiaries are translated at foreign exchange rates prevailing at the balance sheet date. Exchange differences arising from this translation of foreign operations are reported as an item of other comprehensive loss.

Cash and cash equivalents

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

Marketable debt securities

Marketable securities consist of investments with original maturities greater than ninety days. 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 net income; 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 net income.

United Kingdom Research and development tax credit

As a company that carries out extensive research and development activities, the Company seeks to benefit from two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program. 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.

Based on criteria established by U.K. HM Revenue and Customs ("HMRC"), management of the Company expects a proportion of expenditures being incurred in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for research and development tax credits for the 2020 fiscal year. The Company has qualified under the more favorable SME regime for the year ended December 31, 2019 and expects to qualify under the SME regime for the year ending December 31, 2020.

The RDEC and SME credits are not dependent on the Company generating future taxable income or on the ongoing tax status or tax position of the Company. The Company has assessed its research and development activities and expenditures to determine which activities and expenditures are likely to be eligible under the research and development incentive program described above. At each period end, the Company estimates the reimbursement available to the Company based on available information at the time.

The Company recognizes credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expense. The following table below outlines the changes to the research and development tax credit receivable, including amounts recognized as an offset to research and development expense during the period, for the periods ended June 30, 2020 and 2019 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Balance at beginning of period	$ 30,211	$ 16,094	$ 28,644	$ 10,585
Recognition of credit claims as offset to research and development expense	3,614	4,703	7,031	9,939
(Receipt) of credit claims	(1,015)	—	(1,015)	—
Foreign currency translation	(81)	(472)	(1,931)	(199)
Balance at end of period	$ 32,729	$ 20,325	$ 32,729	$ 20,325

As of June 30, 2020, the Company's tax incentive receivable from the U.K. government was $32.7 million, of which $13.0 million was classified as current and $19.7 million was classified as noncurrent. As of December 31, 2019, the Company's tax incentive receivable from the U.K. government was $28.6 million, of which $14.9 million was classified as current, and $13.7 million was classified as noncurrent.

Restricted cash and construction deposits

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on the Company's condensed consolidated balance sheet. The Company has an outstanding letter of credit for $3.0 million associated with a lease, and is required to hold this amount in a standalone bank account, as of June 30, 2020 and December 31, 2019. 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 June 30, 2020, and December 31, 2019.

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

	June 30, 2020	December 31, 2019
	(in thousands)	
Cash and cash equivalents	$ 41,174	$ 19,053
Restricted cash	4,266	4,264
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 45,440	$ 23,317

The Company also has $8.1 million in an escrow account associated with the construction of the Company's leased facility in Fremont, California, which the Company has ceased construction and build-out of and intends to consider its options relating to the lease, including subleasing the facility. Subject to the terms of the lease and reduction provisions, this amount may be decreased to nil over time upon qualifying construction expenditure, or will be returned in late 2022 to the extent funds are not used. The Company deposited $10.0 million into the account in the first quarter of 2020 and has received $1.9 million in receipts from the escrow funds for work performed to date. Of the $8.1 million remaining in the escrow account, $2.3 million is classified within other prepaid expenses and other current assets and $5.9 million is classified within other assets on the condensed consolidated balance sheet based on the timing of when the Company expects to receive the cash from the escrow agent.

Product sales

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

Research and development costs

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

Research agreement costs and accruals

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

Share-based compensation

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

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in shareholders' equity that result from transactions and economic events other than those with shareholders. Reclassifications from other comprehensive loss to income from the sale of investments are not material. The components of accumulated other comprehensive income (loss) are detailed as follows (in thousands):

	Currency Translation	Unrealized Gain (Loss) on Investments	Accumulated Other Comprehensive Income (Loss)
Balance at December 31, 2019	$ 1,776	$ 266	$ 2,042
Other comprehensive (loss) income, net of tax	6,034	(1,021)	5,013
Balance at March 31, 2020	$ 7,810	$ (755)	$ 7,055
Other comprehensive (loss) income, net of tax	610	1,385	1,995
Balance at June 30, 2020	$ 8,420	$ 630	$ 9,050

Leases

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

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

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

Impairment of long-lived assets

Long-lived assets consist of property and equipment and operating lease right-of-use assets. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, as determined in accordance with the related accounting literature.

Strimvelis loss provision

As part of the GSK transaction (as defined in Note 9), the Company is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available (see Note 9). Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company initially recorded a liability associated with the loss contract of $18.4 million in 2018. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with the Strimvelis program and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a credit to research and development expense. The Company has made an estimate of the expected future losses associated with Strimvelis and will adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of the future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for the updated future losses. The following table below outlines the changes to the Strimvelis loss provision for the periods ended June 30, 2020 and 2019 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2020	2019	2020	2019
Balance at beginning of period	$ 4,751	$ 9,111	$ 6,790	$ 10,339
Amortization of loss provision	$ (349)	$ (1,051)	$ (2,018)	$ (2,577)
Foreign currency translation	(10)	(243)	(380)	55
Balance at end of period	$ 4,392	$ 7,817	$ 4,392	$ 7,817

Of the balance as of June 30, 2020 noted in the table above, $0.6 million is classified as current, and $3.8 million is classified as non-current.

Net income (loss) per share

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

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

	As of June 30,	
	2020	2019
Share options	12,343,287	10,972,582
Unvested performance-based restricted share units	680,824	595,422
	13,024,111	11,568,004

Recent Accounting Pronouncements

Recently adopted accounting pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* (“ASU 2016-02”), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). ASU 2016-02 supersedes the lease guidance under FASB ASC Topic 840, *Leases*, resulting in the creation of FASB ASC Topic 842, *Leases* (“ASC 842”). As we are no longer an emerging growth company as of December 31, 2019, ASC 842 became effective for us in 2019, as of January 1, 2019. During the nine months ended September 30, 2019, while the Company was an emerging growth company, ASC 840 was applied to leases. The Company’s previously reported consolidated cash flow statement for the six months ended June 30, 2019 has been recast to reflect adoption of ASC 842 effective January 1, 2019. The following table summarizes the impact of the adoption to the Company’s operating cash flows in the previously issued condensed consolidated statement of cash flows. There was no impact to the condensed consolidated statement of comprehensive loss for the six months ended June 30, 2019 as a result of the adoption of ASC 842. The table also includes other presentation adjustments within operating cash flows made to conform to current period presentation (in thousands):

	As previously reported	ASC 842 adjustments	Other presentation adjustments	As recast
Cash flows from operating activities:	$ (81,269)	$ —	$ —	$ (81,269)
Net loss attributable to ordinary shareholders				
Adjustments to reconcile net loss to net cash used in operating activities:				
Depreciation	775	—	—	775
Non-cash share-based compensation	8,451	—	—	8,451
Non-cash interest expense	46	—	—	46
Amortization of Strimvelis loss provision	(2,589)	—	—	(2,589)
Accretion of discount on marketable securities	(232)	—	—	(232)
Other non-cash adjustments	—	—	2,860	2,860
Changes in operating assets and liabilities:				
Trade receivables	370	—	—	370
Research and development tax credit receivable	(9,913)	—	—	(9,913)
Prepaid expenses, current assets and other assets	1,257	(132)	—	1,125
Operating leases, right-of-use assets	—	1,324	—	1,324
Accounts payable, accrued expenses and other current liabilities	9,784	(122)	(2,860)	6,802
Other long-term liabilities	203	(1,100)	—	(897)
Operating lease liabilities	—	30	—	30
Net cash used in operating activities	$ (73,117)	$ —	$ —	$ (73,117)

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* (“ASU 2016-13”), which requires entities to record expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities in unrealized loss positions, the new standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard became effective for us on January 1, 2020. This guidance did not have a significant impact on the Company’s consolidated financial statements and related disclosures. The Company has a U.K. research and development tax credit receivable that is subject to this guidance; however, there has been no allowance recorded for this receivable.

3. Fair Value Measurements and Marketable Debt Securities

The following tables present information about the Company’s financial assets that have been measured at fair value as of June 30, 2020 and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair value determined by Level 2 inputs utilize observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, quoted market prices in markets that are not active or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities. Fair values determined by Level 3 inputs are unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. During the three months and six months ended June 30, 2020, there were no transfers between Level 1 and Level 2 financial assets.

The following table summarizes the Company's cash equivalents and marketable debt securities as of June 30, 2020, in thousands:

	Fair Value Measurements at June 30, 2020 Using:			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 21,413	$ —	$ —	$ 21,413
U.S. government securities	—	5,000	—	5,000
Total cash equivalents	$ 21,413	$ 5,000	$ —	$ 26,413
Marketable securities				
U.S. government securities	$ —	$ 2,997	$ —	$ 2,997
Corporate bonds	—	155,715	—	155,715
Commercial paper	—	28,768	—	28,768
Total marketable securities	$ —	$ 187,480	$ —	$ 187,480
Total	$ 21,413	$ 192,480	$ —	$ 213,893

The following table summarizes the Company's cash equivalents and marketable debt securities as of December 31, 2019, in thousands:

	Fair Value Measurements at December 31, 2019 Using:			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 202	$ —	$ —	$ 202
U.S. government securities	—	3,159	—	3,159
Corporate bonds	—	9,792	—	9,792
Total cash equivalents	$ 202	$ 12,951	$ —	$ 13,153
Marketable securities				
Corporate bonds	$ —	$ 259,900	$ —	$ 259,900
Commercial paper	—	46,037	—	$ 46,037
Total marketable securities	$ —	$ 305,937	$ —	$ 305,937
Total	$ 202	$ 318,888	$ —	$ 319,090

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

Marketable Debt Securities

The following table summarizes the Company's marketable debt securities as of June 30, 2020, in thousands:

	At June 30, 2020				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
U.S. government securities	$ 8,000	$ —	$ (3)	$ —	$ 7,997
Corporate bonds	155,084	651	(20)	—	155,715
Commercial paper	28,765	7	(4)	—	28,768
Total	$ 191,849	$ 658	$ (27)	$ —	$ 192,480

The following table summarizes the Company's marketable securities as of December 31, 2019, in thousands:

	At December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. government securities	$ 3,159	$ —	$ —	$ 3,159
Corporate bonds	259,669	285	(54)	259,900
Commercial paper	55,794	42	(7)	55,829
Total	$ 318,622	$ 327	$ (61)	$ 318,888

The following table summarizes the Company's available-for-sale debt securities by contractual maturity, as of June 30, 2020 and December 31, 2019, in thousands:

	At June 30, 2020	At December 31, 2019
Due in one year	$ 189,120	$ 250,490
Due after one year through three years	3,360	68,398
Total	$ 192,480	$ 318,888

4. Property and Equipment, Net

Property and equipment, net consisted of the following, in thousands:

	June 30, 2020	December 31, 2019
Property and equipment:		
Lab equipment	$ 4,785	$ 6,377
Leasehold improvements	2,322	1,839
Furniture and fixtures	449	508
Office and computer equipment	296	184
Construction-in-process	737	1,848
Property and equipment	$ 8,589	$ 10,756
Less: accumulated depreciation	(3,129)	(3,160)
Property and equipment, net	$ 5,460	$ 7,596

Depreciation expense was $0.6 million and $0.4 million for the three months ended June 30, 2020 and 2019, respectively Depreciation expense was $1.1 million and $0.8 million for the six months ended June 30, 2020 and 2019, respectively. During the second quarter of 2020, the Company took impairment charges of $2.3 million related to construction-in-process and $0.8 million related to laboratory equipment (See Note 8).

5. Accrued Expenses and Other Liabilities

Accrued expenses and other liabilities consisted of the following, in thousands:

	June 30, 2020	December 31, 2019
Accrued external research and development expenses	$ 8,365	$ 16,215
Accrued payroll and related expenses, including severance	7,759	12,381
Accrued professional fees	1,041	1,321
Accrued other	2,027	5,069
Strimvelis liability - current portion	619	2,994
Total accrued expenses and other liabilities	$ 19,811	$ 37,980

6. Notes Payable

In May 2019, as amended in April 2020, the Company entered into a senior term facilities agreement (the "Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), as agent, and additional lenders from time to time (together with MidCap Financial, the "Lenders"), to borrow up to $75.0 million in term loans. To date, the Company has borrowed $25.0 million under an initial term loan. The remaining $50.0 million under the Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a $25.0 million term loan available no earlier than July 1, 2020 and no later than March 31, 2021 upon submission of certain regulatory filings and evidence of the Company having $100 million in cash and cash equivalent investments; and the third term loan being a $25.0 million term loan available no earlier than July 1, 2020 and no later than September 30, 2021 upon certain regulatory approvals and evidence of the Company having $125 million in cash and cash equivalent investments.

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

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

As of June 30, 2020, and December 31, 2019, notes payable consist of the following (in thousands):

	June 30, 2020	December 31, 2019
Notes payable, net of issuance costs	$ 24,601	$ 24,541
Less: current portion	$ (694)	—
Notes payable, net of current portion	$ 23,907	$ 24,541
Accretion related to final payment	285	158
Notes payable, long term	$ 24,192	$ 24,699

As of June 30, 2020, the estimated future principal payments due are as follows (in thousands):

	Aggregate Minimum Payments
2020 (July - December)	—
2021	4,861
2022	8,333
2023	8,334
Thereafter	4,597
Total	26,125
Less current portion	(694)
Less unamortized portion of final payment	(840)
Less unamortized debt issuance costs	(399)
Notes payable, long term	$ 24,192

During the three months and six months ended June 30, 2020, the Company recognized $0.6 million and $1.2 million of interest expense, respectively, related to the term loan. During the three months and six months ended June 30, 2019 the Company recognized $0.2 million of interest expense related to the term loan. The effective annual interest rate as of June 30, 2020 on the outstanding debt under the term loan was approximately 9.0%.

7. 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 determined not to make any further awards under the 2016 plan following the Company's IPO. As of June 30, 2020, 1,660,560 shares remained available for issuance under the 2018 Plan, and 1,525,904 shares remained available for issuance under the ESPP. In June 2020, the board of directors reserved for issuance 1,000,000 shares under the 2020 Inducement Plan.

Share option activity

The following table summarizes option activity under the plans for three months ended June 30, 2020:

	Number of Options	Weighted Average Exercise Price
Outstanding at December 31, 2019	12,216,140	$ 6.61
Granted	5,080,852	12.25
Exercised	(445,135)	4.84
Forfeited	(1,983,711)	9.95
Outstanding at June 30, 2020	14,868,146	$ 8.13
Vested and expected to vest, as of June 30, 2020	14,868,146	$ 8.13
Exercisable, June 30, 2020	6,639,957	$ 5.15

The weighted-average grant date fair value of share options granted during the six months ended June 30, 2020 was $7.78.

Restricted Share Units

Performance-based restricted share units

The Company has issued performance-based restricted share units ("RSUs") to certain executives and members of its senior management, with vesting linked to the achievement of three specific regulatory and research and development milestones and one market condition based upon the volume weighted-average price ("VWAP") of the Company's ADSs for a certain period. Upon achievement of any of the aforementioned milestones, one third of the RSUs will vest, and the award will become fully vested upon achievement of three of the four performance conditions.

CEO Award

The Company granted 195,000 performance-based RSUs to its Chief Executive Officer in April 2020. The award vests on January 2, 2024 as to 1/3 of the award for each of the first three to occur of four milestones, if each such milestone is achieved by the Company on or before December 31, 2023 and Dr. Gaspar remains continuously employed with the Company through January 2, 2024. The milestones relate to achievement of specific clinical and regulatory milestones.

The following table summarizes award activity for the six months ended June 30, 2020:

	Shares	Weighted Average Grant Date Fair Value
Unvested and outstanding at December 31, 2019	556,422	$ 13.58
Granted	195,000	7.01
Vested	—	
Forfeited	(265,672)	14.98
Unvested and outstanding at June 30, 2020	485,750	$ 10.18

The maximum aggregate total fair value of all outstanding RSUs is $7.3 million. The fair value associated with the performance-based conditions will be recognized when achievement of the milestones becomes probable, if at all. The Company determined that, as of June 30, 2020, none of the regulatory and research and development milestones associated with any outstanding RSUs were deemed probable. The amount of compensation cost recognized for the six months ended June 30, 2020 and 2019 for the market condition associated with the performance-based RSUs was $0.3 million and $0.6 million, respectively. The amount of compensation cost recognized for the three months ended June 30, 2020 and 2019 for the market condition associated with the performance-based RSUs was $0.1 million and $0.3 million, respectively.

Share-based compensation expense

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

	Three months ended June 30,		Six months ended June 30,	
	2020	2019	2020	2019
Research and development	$ 2,671	$ 1,653	$ 5,781	$ 2,970
General and administrative	3,408	2,977	9,777	5,481
Total share-based compensation	$ 6,079	$ 4,630	$ 15,558	$ 8,451

During the six months ended June 30, 2020, the Company recognized $2.7 million of share-based compensation expense to selling, general and administrative expense related to the modification of share option awards associated with the separation of the Company's former Chief Executive Officer.

As of June 30, 2020, total unrecognized compensation cost related to unvested share option grants was approximately $61.0 million. This amount is expected to be recognized over a weighted average period of approximately 2.9 years. As of June 30, 2020, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $5.7 million, dependent upon achievement of the aforementioned milestones.

8. Restructuring charges

On May 4, 2020, the Company committed to a new strategic plan and restructuring intended to enable the Company to advance its corporate strategy while reducing overall operating expenses, including ceasing construction and build-out of its Fremont, California manufacturing facility, closing its office in Menlo Park, California, reducing its workforce by approximately 25% across the Company, eliminating a number of future positions expected to be recruited in 2020 and 2021, reducing its investment in the future development for certain programs, and other cost-saving measures (collectively, the "Restructuring"). The workforce reductions will take place primarily during the second and third quarters of 2020.

Cash restructuring charges

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

	Employee termination benefits
Balance at December 31, 2019	$ —
Charged to expense	1,589
Payments made	(748)
Balance at June 30, 2020	$ 841

During the six months ended June 30, 2020, $1.1 million of the employee termination benefits has been classified on the condensed consolidated statement of operations as research and development expense and $0.5 million has been classified as selling, general, and administrative expense.

Impairment of long-lived assets

During the three months and six months ended June 30, 2020, the Company also took the following non-cash charges to research and development expense associated with the impairment of construction-in-process associated with the Fremont manufacturing facility, partial impairment of the right-of-use asset for the Fremont manufacturing facility lease (the “Fremont ROU asset”), and a write-down of laboratory equipment from the Company’s Menlo Park, CA facility, in thousands:

	Asset write-downs
Operating lease right-of-use asset	$ 2,605
Construction-in-process	2,285
Laboratory equipment	760
Charge taken to research and development expense	5,650

The Company assessed the Fremont construction-in-process for impairment in May 2020 upon the Restructuring. The construction-in-process related to design costs, and was determined to have no potential future value, and an impairment charge of $2.3 million was taken for the full value of the construction-in-process asset.

The Company assessed the Fremont ROU asset for impairment in May 2020 upon the Restructuring when the carrying value of the asset was $13.8 million. The Fremont ROU asset represented the asset group for the impairment assessment. Upon failing the first step of the long-lived asset impairment model where the undiscounted cash flows were less than the carrying value of the Fremont ROU asset, the Company performed the second step by comparing the fair value of the Fremont ROU asset to its carrying value. The fair value of the Fremont ROU asset is a non-recurring fair value measurement that was measured using a probability-weighted discounted cash flow approach, which estimated the present value of potential sublease income to be generated by the facility, less costs incurred to sublease the facility. The significant assumptions inherent in estimating the various probability weighted scenarios included the undiscounted forecasted sublease income less costs incurred, which included assumptions of the expected income and timing of entering into a future sublease, and a market-participant discount rate that reflects a potential discount rate. The Company selected the assumptions used in the fair value estimate using current market data associated with the potential sublease income and market participant discount rates. The undiscounted cash flows utilized in the fair value estimate ranged from $11.7 million to $19.1 million to be generated over the remainder of the lease term. The market-participant discount rate utilized in the fair value estimate was 4.6%. These assumptions represent level 3 inputs of the fair value hierarchy (see Note 3).

As of the assessment date, the fair value of the Fremont ROU asset was $11.2 million, and the Company recorded a $2.6 million impairment charge related to the asset. The remaining carrying value of the Fremont ROU asset will be amortized over the remaining lease term on a straight-line basis. A triggering event identified for the Fremont ROU asset in future periods could result in additional impairment charges if the estimated fair value of the asset is determined to be lower than the carrying value.

9. License Agreements

GSK asset purchase and license agreement

In April 2018, the Company completed an asset purchase and license agreement (the “GSK Agreement”) with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon Foundation and San Raffaele Hospital (“Telethon-OSR”). The portfolio of programs and options acquired consisted of two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS, one earlier stage clinical gene therapy program for TDT, Strimvelis, and option rights exercisable upon completion of clinical proof of concept studies for three additional earlier-stage development programs, which option rights have all subsequently lapsed. The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations, resulting in total consideration of $ 133.6 million, which was recorded in the second quarter of 2018.

The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher (“PRV”) from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDT, the first of which GSK retained beneficial ownership over. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As part of the GSK Agreement the Company is also required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as the Company’s OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site.

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and the Company-developed product candidate, OTL-101. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and OTL-101. The Company will also pay tiered royalty rates at a percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at a percentage from the high single-digits to low double-digit for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones applicable to GSK. The Company’s royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company’s royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

Telethon-OSR research and development collaboration and license agreements

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

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

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

Oxford BioMedica license, development and supply agreement

In November 2016, and amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica plc whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and whereby Oxford BioMedica will provide process development services ("Oxford BioMedica Development Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Development Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and fourth milestones were achieved, and the Company issued 150,826 ordinary shares. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million. The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

10. Income Taxes

Deferred tax assets and deferred tax liabilities are determined based on temporary differences between the financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is recorded against deferred tax assets if it is more likely than not that some portion or all of the deferred tax assets will not be realized.

The Company does not recognize a tax benefit for uncertain tax positions unless it is more likely than not that the position will be sustained upon examination by tax authorities, including resolution of any related appeals or litigation processes, based on the technical merits of the position. The tax benefit that is recorded for these positions is measured at the largest amount of cumulative benefit that has greater than a 50 percent likelihood of being realized upon ultimate settlement. Deferred tax assets that do not meet these recognition criteria are not recorded and the Company recognizes a liability for uncertain tax positions that may result in tax payments. If such unrecognized tax benefits were realized and not subject to valuation allowances, the entire amount would impact the tax provision. The Company has not recorded any amounts for unrecognized tax positions as of June 30, 2020 or December 31, 2019.

In response to the COVID-19 pandemic, the Coronavirus Aid, Relief and Economic Security Act (CARES Act) was signed into law in March 2020. The CARES Act lifts certain deduction limitations originally imposed by the Tax Cuts and Jobs Act of 2017 (2017 Tax Act). The CARES Act provides that corporate taxpayers may carryback net operating losses (NOLs) originating during 2018 through 2020 for up to five years to recover taxes paid in prior years, eliminates the 80% of taxable income limitations by allowing corporate entities to fully utilize NOL carryforwards to offset taxable income in 2018, 2019 or 2020. Taxpayers may generally deduct interest up to the sum of 50% of adjusted taxable income plus business interest income (30% limit under the 2017 Tax Act) for tax years beginning January 1, 2019 and 2020. The CARES Act allows taxpayers with alternative minimum tax credits to claim a refund in 2020 for the entire amount of the credits instead of recovering the credits through refunds over a period of years, as originally enacted by the 2017 Tax Act. In addition, the CARES Act raises the corporate charitable deduction limit to 25% of taxable income and makes qualified improvement property generally eligible for 15-year cost-recovery and 100% bonus depreciation. The enactment of the CARES Act did not result in any material adjustments to the Company's income tax provision for the three months ended June 30, 2020, or to the Company's net deferred tax assets as of June 30, 2020.

The Company recorded income tax benefit of $0.3 million and $0.2 million for the six months ended June 30, 2020 and 2019, respectively. The Company recorded and income tax expense of $0.1 million and benefit of $0.8 million for the three months ended June 30, 2020 and 2019, respectively, which relates primarily to the Company's subsidiary operations in Europe and the U.S.

11. Commitments and Contingencies

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

12. Employee Benefit Plans

The Company makes contributions to private defined contribution employee benefit plans on behalf of its employees. The Company provides employee contributions of up to six percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid $0.3 million and $1.0 million in matching contributions for the three months and six months ended June 30, 2020. The Company paid $0.3 million and $0.6 million in matching contributions for the three months and six months ended June 30, 2019.

13. Related Party Transactions

GSK

In April 2018, the Company completed the GSK Agreement with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon-OSR (See Note 9).

As of June 30, 2020, and December 31, 2019, the Company had accounts payable and accrued expenses due to GSK of $5.1 million and $3.3 million, respectively. During the six months ended June 30, 2020 the Company entered into a global license agreement with GSK for use of their lentiviral stable cell line technology whereby we recorded $1.3 million of in-process research and development expense associated with upfront payments made to GSK. During the six months ended June 30, 2020, the Company made $0.6 million in payments on accounts payable due to GSK, and the Company incurred immaterial royalties due to GSK associated with sales of Strimvelis.

14. Subsequent Events

On July 2, 2020 (the "Effective Date"), the Company entered into a manufacturing and technology development master agreement (the "Agreement") with MolMed S.p.A. ("MolMed"), pursuant to which MolMed will develop, manufacture and supply certain viral vectors and conduct cell processing activities for certain Orchard development and commercial programs. Under the terms of the Agreement, the Company is obligated to pay MolMed a minimum product manufacturing commitment of €2.7 million per annum for the term of the Agreement, which may increase to the mid-seven figures per annum upon the achievement of certain milestones that may require additional manufacturing capacity. Additionally, the Company has committed €10.4 million per annum for dedicated manufacturing and development resources, including exclusive manufacturing suites within MolMed's existing facilities, which the Company may increase or decrease on a rolling basis with between six and 12-months' prior written notice to MolMed.

The Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The Agreement may be extended for an additional two years by mutual agreement of the Company and MolMed. The Company has the right to terminate the Agreement at its discretion upon 12-month's prior written notice to MolMed, and beginning no earlier than July 2, 2022, MolMed has the right to terminate the Agreement at its discretion upon 24-month's prior written notice to the Company. Each party may terminate the Agreement upon prior notice to the other party for an uncured material breach that the breaching party does not cure within the notice period.

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. Some of the information contained in this discussion and analysis and set forth elsewhere in this Quarterly Report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in Part II—Item 1A. of this Quarterly Report for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Business Overview

Orchard Therapeutics is a global gene therapy leader dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. We have one of the deepest and most advanced gene therapy product candidate 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. We recently announced a new strategic plan and restructuring intended to enable us to advance our corporate strategy while reducing overall operating expenses, including reducing our investment in the future development of OTL-101 for ADA-SCID and OTL-300 for TDT, among other measures.

Since our inception in 2015, we have devoted substantially all of our resources to conducting research and development of our product candidates, in-licensing and acquiring rights to our product candidates, business planning, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of equity securities, including ADSs and convertible preferred shares. Through June 30, 2020, we had received net proceeds of $335.1 million from sales of ADSs in our initial public offering and follow-on public offering, $283.4 million from sales of our convertible preferred shares, and $24.5 million from our senior term facilities agreement (the "Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial").

We have incurred significant operating losses since our inception. With the exception of our commercial product Strimvelis®, which was acquired in April 2018, we will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. Our net losses were $98.1 million and $81.3 million for the six months ended June 30, 2020 and 2019, respectively. As of June 30, 2020, and December 31, 2019, we had an accumulated deficit of $551.7 million and $453.7 million, respectively. As of June 30, 2020, we had cash, cash equivalents, marketable securities and restricted cash of $232.9 million, excluding amounts held in escrow deposits. Our losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future.

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

Recent Developments

Business update regarding COVID-19

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

In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy, have placed significant restrictions on travel. While some restrictions have been relaxed since the beginning of the pandemic, many restrictions are still in place. In the U.S. and U.K, our office-based employees have been working from home since early March 2020. Limitations on travel and other social distancing measures may have an effect on our preclinical and clinical activities and regulatory timelines. While our clinical sites are still treating patients in studies for OTL-201, OTL-103 and OTL-200 (for the treatment of mucopolysaccharidosis type IIIA (MPS-IIIA), Wiskott Aldrich syndrome (WAS) and metachromatic leukodystrophy (MLD), respectively), these centers are also devoting significant resources to patients with COVID-19, which could limit their ability to enroll additional patients in ongoing clinical studies. While we believe we have enrolled and treated enough patients to support regulatory filings for OTL-200 in the U.S. and EU, COVID-19-related impacts could shift the enrollment timeline for our OTL-201 trial for the treatment of MPS-IIIA by up to three months.

Travel and stay-at-home orders could adversely affect our contract manufacturers and third-party logistics providers. To date, our third-party contract development and manufacturing organization (CDMO) partners have continued to operate at or near normal levels. While we currently do not anticipate any interruptions, it is possible that the COVID-19 pandemic and response efforts may have an impact in the future on our and/or our third-party suppliers and CDMO partners' ability to manufacture our products in development. The treatment site for Strimvelis®, our European Medicines Agency-approved gene therapy for the treatment of ADA-SCID, initially postponed scheduling and treating any non-urgent patients with the therapy; however, treatments resumed in June 2020. We have reviewed the collectability and valuation of our assets through the date of financial statement issuance and did not identify any significant recoverability concerns or impairments. Any prolonged material disruptions to our employees, suppliers, CDMOs, vendors, or patients could impact our operating results and could lead to impairments. To date the Company has recorded impairments on long-lived assets that are due to a combination of a corporate restructuring and COVID-19 market impacts (see Note 8 of condensed consolidated financial statements). The capital markets have experienced significant volatility as a result of the pandemic and our ability to access the capital markets could be impacted if disruptions in the capital markets continue.

For additional information on the various risks posed by the COVID-19 pandemic, please the section titled "Item 1A. Risk Factors" included in this report.

Strategic plan and restructuring

In May 2020, we announced a new strategic plan and restructuring intended to enable us to advance our corporate strategy while reducing overall operating expenses, which includes decisions to:

- Reduce our investment in OTL-101 for ADA-SCID and OTL-300 for TDT and reallocate financial resources to other programs, although we will continue to advance ongoing clinical trials and any required regulatory updates for these indications.
- Accelerate research and development projects in less rare indications, including two new research programs in genetic subsets of frontotemporal dementia (FTD) and Crohn's disease.
- Close our California operations, including our office in Menlo Park, California, and consolidate our research and development teams to a single site. We believe this consolidation will reduce overall costs and provide greater efficiency in the development process at a location closer to our existing CDMO partners. In the second quarter of 2020 we took a $0.8 million restructuring charge associated with the write-down of laboratory equipment from the Menlo Park site.
- Cease the construction and build-out of a manufacturing facility in Fremont, California. We intend to continue to rely on our network of CDMOs for our manufacturing needs as we review the potential development of long-term in-house manufacturing capabilities should our product candidates achieve commercial success. We will consider our options relating to the lease, including subleasing the facility. During the second quarter of 2020 we recorded a $2.6 million impairment charge on the Fremont facility operating lease right-of-use asset and recorded a $2.3 million impairment on construction-in-process associated with construction design costs on the facility.
- Reduce our headcount globally by approximately 25% to align with our revised organizational priorities, and eliminate a number of future positions expected to be recruited in 2020 and 2021. We estimate that we will incur aggregate charges of $2.1 million in the second and third quarters of 2020 as a result of the headcount reductions, consisting of one-time cash expenditures for severance and employee termination-related costs.

We currently expect that the net effect of our new strategic plan and restructuring will result in approximately $125.0 million in cost savings in 2020 and 2021, but there can be no assurance that we will achieve all of these cost savings

Components of our results of operations

Revenue

We do not expect to generate any significant revenue from the sale of products, with the exception of Strimvelis, in the near future. Our product candidate, OTL-200, for the treatment of MLD is currently under review with the European Medicines Agency (EMA) and we expect a regulatory decision on approval in 2020. If OTL-200 is approved by the EMA and we are able to identify patients and secure reimbursement for our treatment, we will begin to generate revenue from the sale of OTL-200 in Europe. If our development efforts for other product candidates that we may develop in the future are successful and result in regulatory approval, or collaboration or license agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from collaboration or license agreements.

During the three months and six months ended June 30, 2020, we recognized $0.6 million and nil revenue from sales of Strimvelis. Strimvelis is currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. We expect that product sales of Strimvelis will fluctuate quarter over quarter, in particular as we continue to promote the product and increase market access. As a result of the COVID-19 global pandemic, the San Raffaele Hospital postponed scheduling and treating non-urgent patients with Strimvelis, which may impact the timing of future Strimvelis revenues. Net product sales of $0.6 million for the quarter ended June 30, 2020 may not be representative of our sales for any future period.

Cost of product sales

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

Operating expenses

Research and development expenses

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

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

We expense research and development cost as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as a prepaid expense or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. Amortization of the Strimvelis loss provision is also recorded as an offset to research and development expense (See Note 2 of our condensed consolidated financial statements).

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

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

During the second quarter of 2020, we also took $5.6 million in non-cash charges to research and development expense associated with the impairment of construction-in-process associated with the Fremont manufacturing facility, partial impairment of the operating lease right-of-use asset for the Fremont facility, and a write-down of laboratory equipment from our Menlo Park, CA facility. We also expect to incur additional expenses related to milestone, royalty payments and maintenance fees payable to third parties with whom we have entered into license agreements to acquire the rights related to our product candidates.

The successful development of our product candidates and commercialization of Strimvelis and our product candidates, if approved, is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the following:

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

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA, EMA or another regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant trial delays due to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development and we may never succeed in obtaining regulatory approval for any of our product candidates.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, commercial, corporate and business development, and administrative functions. Selling, general and administrative expenses also include professional fees for legal, patent, accounting, auditing, tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

We expect that our selling, general and administrative expenses will increase in the future as we increase our selling, general and administrative headcount to support our continued research and development and potential commercialization of our portfolio of product candidates. In addition, we are expanding our organization into multiple countries in Europe to support the potential commercialization of OTL-200 for MLD, which is currently under regulatory review by the EMA. We also expect to incur increased expenses associated with compliance with our obligations as a public company, including costs of accounting, audit, legal, regulatory and tax compliance services, director and officer insurance costs and investor and public relations costs.

In the first quarter of 2020, we recorded a $3.4 million charge to selling, general, and administrative expenses associated with the separation of our former Chief Executive Officer. Of this charge, there was $0.7 million associated with cash benefits, and $2.7 million non-cash charge associated with the modification of share options. In the second quarter of 2020, we incurred $0.5 million in employee termination benefits associated with headcount reductions made in connection with our new strategic initiatives and related restructuring.

Other income (expense), net

Interest income

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

Interest expense

Interest expense consists of interest associated with our Credit Facility with MidCap Financial, which we entered into in May 2019. The Credit Facility bears a variable interest rate at a rate of 6.0% above LIBOR, plus a final payment equal to 4.5% of the principal borrowed under the Credit Facility. In fiscal year 2020, we will have a full year of interest expense, as compared to 7 months in 2019.

Other income (expense)

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

Results of operations

Comparison of the six months ended June 30, 2020 and 2019

The following table summarizes our results of operations for the six months ended June 30, 2020 and 2019:

	Six Months Ended June 30,		
	2020	2019	Change
	(in thousands)		
Product sales, net	$ 597	$ —	$ 597
Costs and operating expenses			
Cost of product sales	191	—	191
Research and development	56,404	57,971	(1,567)
Selling, general and administrative	35,804	24,464	11,340
Total costs and operating expenses	92,399	82,435	9,964
Loss from operations	(91,802)	(82,435)	(9,367)
Other income (expense):			
Interest income	2,372	3,350	(978)
Interest expense	(1,181)	(245)	(936)
Other income (expense):	(7,733)	(2,118)	(5,615)
Total other income (expense), net	(6,542)	987	(7,529)
Loss before provision for income taxes	(98,344)	(81,448)	(16,896)
Income tax (expense) benefit	275	179	96
Net loss attributable to ordinary shareholders	$ (98,069)	$ (81,269)	$ (16,800)

Research and development expenses

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

	Six months ended June 30,		
	2020	2019	Change
	(in thousands)		
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 10,451	$ 23,685	$ (13,234)
Primary immune deficiencies	11,791	15,850	(4,059)
Blood disorders	1,152	1,915	(763)
Other research and preclinical programs under development	934	102	832
Total direct research and development expenses:	24,328	41,552	(17,224)
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	19,801	13,657	6,144
Share-based compensation	5,781	2,970	2,811
Accretion of Strimvelis loss provision	(2,018)	(2,588)	570
Research and development tax credit	(7,031)	(9,939)	2,908
Impairment of long-lived assets	5,650	—	5,650
Facility and other	9,893	12,319	(2,426)
Total indirect research and development expenses	32,076	16,419	15,657
Total research and development expenses	$ 56,404	$ 57,971	$ (1,567)

Direct research and development expenses for our neurometabolic disorder programs decreased by $13.2 million. Direct expenses associated with OTL-203 for MPS-I declined by $15.3 million, primarily due to $17.2 million in combined upfront and milestone payments made to Telethon Foundation and San Raffaele Hospital (“Telethon-OSR”) to license the program in 2019 that were not repeated in 2020. This decline was offset by an increase of $1.8 million in direct expenses associated with our proof-of-concept trial for OTL-203. Direct expenses associated with OTL-200 for MLD increased by $2.2 million compared to the first half of 2019. This was primarily due to an increase of $1.9 million in manufacturing costs associated with the build-up of pre-launch inventory. Direct expenses for OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB did not change materially as compared to the prior year period.

Direct research and development expenses for primary immune deficiency-related programs declined by $4.1 million, primarily due to the de-prioritization of OTL-101 for ADA-SCID. Direct expenses associated with OTL-101 declined by $4.6 million. This was due to a $2.4 million decrease in manufacturing and process development costs with third-party contract manufacturers, and a $1.1 million decline in clinical costs as compared to the first half of 2019. We expect that OTL-101 costs will continue to decline compared to the 2019 as we reduce our investment and development in the program. The decline in direct expenses for OTL-101 were offset by an increase in direct expenses for OTL-102 for X-CGD of $1.2 million, which was primarily due to by a payment in the form of ordinary shares valued at $0.8 million made to Oxford BioMedica upon entering into an amendment to an on-going agreement. Direct expenses for Strimvelis declined $0.2 million as compared to the first half of 2019 due to lower clinical costs.

Direct research and development expenses for our blood disorder programs declined by $0.8 million due to lower expenses for OTL-300. The decline in costs is due to a $0.5 million decline in manufacturing costs, a $1.1 million decline in clinical costs, and $0.2 million decline in consulting-related expenses. These declines were offset by $1.0 million in milestone payments related to the program. We expect that OTL-300 costs will continue to decline compared to the prior year as we reduce our investment and development in the program.

The increase in costs associated with other research and preclinical programs relates to costs associated with having additional early-stage programs in our pipeline in 2020 compared to 2019, including programs targeting frontotemporal dementia and Crohn’s disease. We expect these costs to continue to increase as part of our new strategic growth plan to focus on these less rare indications.

Unallocated research and development costs and offsets to research and development expenses increased by $15.7 million. This is due to $5.6 million non-cash impairment charges associated with the consolidation and closure of our research and development and manufacturing facilities in California. These charges included a $2.6 million impairment associated with the Fremont facility right-of-use asset, $2.3 million in design costs associated with the Fremont facility, and $0.8 million in impairment of laboratory equipment. Personnel costs also increased by $6.1 million and share-based compensation increased by $2.8 million. The personnel and share-based compensation increases are attributable to an increased headcount year-over-year and $1.1 million in severance-related charges associated with our restructuring. These increases were offset by a decline of $2.4 million in other research and development costs such as lab supplies and consumables, external manufacturing and process development, and other unallocated platform-related costs not attributable to a specific developmental program. This decline was primarily due to a decline in platform-related manufacturing and clinical costs, and other professional and consulting expenses. The increases noted above were further offset by $7.0 million as a result of the benefits of the U.K. research and development tax credit that is recorded as an offset to research and development expense. Tax credit benefits declined by $2.9 million in the first half of 2020 compared to the first half of 2019, as we have maximized the tax credit available for some programs. Accretion of the Strimvelis loss provision, which is also accounted for as an offset to research and development expense declined by $0.6 million in the first half of 2020 as compared to the first half of 2019, as we have adjusted our ongoing estimate due to the de-prioritization of OTL-101 and have extended out the expected period of losses for Strimvelis, which results in lower amortization of the loss provision.

Selling, general and administrative expenses

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

	Six months ended June 30,		
	2020	2019	Change
		(in thousands)	
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 12,933	$ 8,191	$ 4,742
Share-based compensation	9,777	5,481	4,296
Consulting, professional, and insurance-related costs	5,820	4,584	1,236
Marketing, promotions, and advocacy	3,994	2,728	1,266
Facilities and IT-related costs	2,786	2,622	164
Other	494	858	(364)
Total selling, general, and administrative expenses:	$ 35,804	$ 24,464	$ 11,340

Selling, general and administrative expenses were $35.8 million in the first half of 2020, compared to $24.5 million in the first half of 2019. The increase of $11.3 million was primarily due to increased personnel-related costs of $4.7 million from an increased headcount in our selling, general and administrative functions as we prepare for potential launch of OTL-200 for MLD. Included in this increase is a $0.7 million charge associated with the separation of our former Chief Executive Officer in the first quarter of 2020. Share-based compensation expense increased by $4.3 million in the first half of 2020 compared to the first half of 2019 due to the higher number of employees receiving grants, as well as $2.7 million charge associated with the separation of our Chief Executive Officer in March 2020. Consulting, professional, and insurance-related costs increased by $1.2 million, primarily due to an increase in directors' and officers' insurance costs, and increased audit, accounting, and legal fees. Expenses associated with marketing and commercialization of Strimvelis, and costs associated with increased promotional and advocacy activities in preparation for the potential future commercialization of our product candidates, if approved, increased by $1.3 million. These costs were offset by a $0.2 million decline in facilities, IT, and other general and administrative expenses.

Other income (expense), net

Other income (expense), net for the first half 2020 and 2019 consisted of expenses of $6.5 million and income of $1.0 million, respectively. During the first half of 2020, we had realized and unrealized losses on foreign currency transactions of $7.7 million, compared to realized and unrealized losses of $2.1 million for 2019. These unrealized losses are driven primarily by intercompany balances denominated in currencies other than our functional currency, the U.S. Dollar. Additionally, we had interest income of $2.4 million in the first half of 2020, compared to $3.4 million in the first half of 2019. This decline in interest income is attributable to market conditions associated with our marketable debt securities. Interest expense increased by $1.0 million in the first half of 2020 as compared to the first half of 2019, and is attributable to our Credit Facility, which we entered into in May 2019 and was therefore not in place in the entire first half of 2019.

Comparison of the three months ended June 30, 2020 and 2019

The following table summarizes our results of operations for the three months ended June 30, 2020 and 2019:

	Three Months Ended June 30,		
	2020	2019	Change
		(in thousands)	
Product sales, net	$ 597	$ —	$ 597
Costs and operating expenses			
Cost of product sales	191	—	191
Research and development	31,568	40,478	(8,910)
Selling, general and administrative	15,659	13,674	1,985
Total costs and operating expenses	47,418	54,152	(6,734)
Loss from operations	(46,821)	(54,152)	7,331
Other income (expense):			
Interest income	892	1,727	(835)
Interest expense	(568)	(245)	(323)
Other income (expense):	(943)	1,368	(2,311)
Total other income (expense), net	(619)	2,850	(3,469)
Loss before provision for income taxes	(47,440)	(51,302)	3,862
Income tax (expense) benefit	(60)	772	(832)
Net loss attributable to ordinary shareholders	$ (47,500)	$ (50,530)	$ 3,030

Research and development expenses

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

	Three months ended June 30, 2020	2019	Change
	(in thousands)		
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 5,719	$ 21,500	$ (15,781)
Primary immune deficiencies	7,422	7,734	(312)
Blood disorders	970	1,148	(178)
Other research and preclinical programs under development	365	29	336
Total direct research and development expenses:	14,476	30,411	(15,935)
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	9,536	6,949	2,587
Share-based compensation	2,671	1,653	1,018
Accretion of Strimvelis loss provision	(349)	(1,063)	714
Research and development tax credit	(3,648)	(4,702)	1,054
Impairment of long-lived assets	5,650	—	5,650
Facility and other	3,232	7,230	(3,998)
Total indirect research and development expenses	17,092	10,067	7,025
Total research and development expenses	$ 31,568	$ 40,478	$ (8,910)

Direct research and development expenses for our neurometabolic disorder programs decreased by $15.7 million. Direct expenses associated with OTL-203 for MPS-I declined by $16.0 million, primarily due to $17.2 million in combined upfront and milestone payments made to Telethon Foundation and San Raffaele Hospital (“Telethon-OSR”) to license the program in 2019. This decline was offset by an increase of $1.1 million in direct expenses associated with our proof-of-concept trial for OTL-203. Direct expenses associated with OTL-200 for MLD increased by $0.8 million compared to the second quarter of 2019. This was primarily due to an increase of $1.5 million in manufacturing costs associated with the build-up of pre-launch inventory, offset by a $0.5 million decline in clinical trial costs and $0.2 million decline in consulting and other related costs. Direct expenses for OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB declined by $0.5 million due to lower clinical costs.

Direct research and development expenses for primary immune deficiency-related programs declined by $0.3 million, primarily due to the de-prioritization of OTL-101 for ADA-SCID. Direct expenses associated with OTL-101 declined by $1.6 million. This was due to a $0.9 million decrease in manufacturing and process development costs with third-party contract manufacturers, a $0.6 million decline in consulting expenses, and a $0.1 million decline in clinical costs as compared to the second quarter of 2019. We expect that OTL-101 costs will continue to decline compared to the 2019 as we reduce our investment and development in the program. The decline in direct expenses for OTL-101 were offset by an increase in direct expenses for OTL-102 for X-CGD of $1.2 million, which was primarily due to a payment in the form of ordinary shares valued at $0.8 million made to a third-party contract manufacturer upon entering into an amendment to an on-going agreement as well as a $0.4 million increase in clinical and manufacturing costs. Direct expenses for Strimvelis were generally flat as compared to the second quarter of 2019.

Direct research and development expenses for blood disorder-related programs declined by $0.2 million due to lower expenses for OTL-300. The decline in costs is due to a $0.5 million decline in manufacturing costs, and a $0.6 million decline in clinical costs, offset by $0.9 million in milestone payments related to the program. We expect that OTL-300 costs will continue to decline compared to 2019 as we reduce our investment and development in the program. The increase in costs associated with other research and preclinical programs relates to costs associated with having additional early-stage programs in our pipeline in 2020 compared to 2019, including programs targeting frontotemporal dementia and Crohn’s disease. We expect these costs to continue to increase as part of our new strategic growth plan to focus on these less rare indications.

Unallocated research and development costs and offsets to research and development expenses increased by $7.0 million. This is primarily due to $5.6 million non-cash impairment charges associated with the consolidation and closure of our research and development and manufacturing facilities in California. These charges included a $2.6 million impairment associated with the Fremont facility right-of-use asset, $2.3 million in design costs associated with the Fremont facility, and $0.8 million in impairment of laboratory equipment. Personnel costs also increased by $2.6 million and share-based compensation increased by $1.0 million. The personnel and share-based compensation increases are attributable to an increased headcount year-over-year and include $1.1 million in employee termination-related severance charges associated with our restructuring. Further, other research and development costs such as lab supplies and consumables, platform-related external manufacturing and process development, and other unallocated costs not directly attributable to a specific developmental program declined by $4.0 million in the second quarter of 2020 compared to the second quarter of 2019. Included in this decline is a $2.6 million decrease in unallocated platform-related manufacturing and clinical costs, as well as $0.7 million decline in other professional and consulting expenses. The increases noted above were offset by $3.7 million as a result of the benefits of the U.K. research and development tax credit that is recorded as an offset to research and development expense. Tax credit benefits declined by $1.1 million in the second quarter of 2020 compared to the second quarter of 2019, as we have maximized the tax credit available for some programs. Accretion of the Strimvelis loss provision, which is also accounted for as an offset to research and development expense declined by $0.7 million in the second quarter of 2020 as compared to the second quarter of 2019, as we have adjusted our ongoing estimate due to the de-prioritization of OTL-101 and have extended out the expected period of losses for Strimvelis, which results in lower amortization of the loss provision.

Selling, general and administrative expenses

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

	Three months ended June 30,		
	2020	2019	Change
		(in thousands)	
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 6,175	$ 4,346	$ 1,829
Share-based compensation	3,408	2,977	431
Consulting, professional, and insurance-related costs	2,941	2,744	197
Marketing, promotions, and advocacy	1,845	1,418	427
Facilities and IT-related costs	1,164	1,366	(202)
Other	126	823	(697)
Total selling, general, and administrative expenses:	$ 15,659	$ 13,674	$ 1,985

Selling, general and administrative expenses were $15.7 million in the second quarter of 2020, compared to $13.7 million in the second quarter of 2019. The increase of $2.0 million was primarily due to increased personnel-related costs of $1.8 million from an increased headcount in our selling, general and administrative functions as we prepare for potential launch of OTL-200 for MLD. Share-based compensation expense increased by $0.4 million in the second quarter of 2020 compared to the second quarter of 2019 due to the higher number of employees receiving grant. Consulting, professional, and insurance-related costs increased by $0.2 million and relate to ongoing costs of operating as a public company. Expenses associated with marketing and commercialization of Strimvelis, and costs associated with increased promotional and advocacy activities in preparation for the potential future commercialization of our product candidates, if approved, increased by $0.4 million. These increases were offset by declines in facilities and IT costs, as well as declines in unallocated selling, general, and administrative expenses.

Other income (expense), net

Other income (expense), net for the second quarter of 2020 and 2019 consisted of expenses of $0.7 million and income of $2.9 million, respectively. During the second quarter of 2020, we had realized and unrealized losses on foreign currency transactions of $0.9 million, compared to realized and unrealized gains of $1.4 million for 2019. These unrealized losses are driven primarily by intercompany balances denominated in currencies other than our functional currency, the U.S. Dollar. Additionally, we had interest income of $0.9 million in the second quarter of 2020, compared to $1.7 million in the second quarter of 2019. This change is primarily driven by market interest rates on our portfolio of marketable debt securities. Further, we had interest expense of $0.6 million in the second quarter of 2020, compared to $0.2 million in the second quarter of 2019. The increase in interest expense of $0.4 million in the second quarter of 2020 is attributable to our Credit Facility, which we entered into in May 2019 and was therefore not in place in the full second quarter of 2019.

Liquidity and capital resources

From our inception through June 30, 2020, we have not generated significant revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We currently have only one commercial product, Strimvelis, which we acquired from GSK in April 2018 and our product candidates are in various phases of preclinical and clinical development. OTL-200 is currently under regulatory review by the EMA and we expect a decision in the second half of 2020. We do not expect to generate significant revenue from sales of any products in 2020 and until we have obtained additional regulatory approvals, secured broader reimbursement and gained product acceptance. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our initial public offering and follow-on offering, proceeds from the sale of convertible preferred shares, reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine ("CIRM"), and our Credit Facility.

On February 27, 2020, we entered into a Sales Agreement with Cowen and Company, LLC, as agent, relating to an “at the market offering,” pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. As of June 30, 2020, we have not sold any shares under the Sales Agreement.

Through June 30, 2020, we have received net proceeds of $335.1 million from the sale of ADSs in our initial public offering and follow-on offering, net proceeds of $283.4 million from sales of convertible preferred shares, $24.5 million in net proceeds from our Credit Facility, and reimbursement of $7.9 million from our agreement with CIRM, which was formerly a subcontract agreement with UCLA. As of June 30, 2020, we had cash, cash equivalents, and marketable securities of $228.7 million, excluding restricted cash and construction deposits in escrow.

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 on Form 10-K, filed with the SEC on February 27, 2020.

Cash flows

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

	Six months ended June 30, 2020	Six months ended June 30, 2019
	(in thousands)	
Net cash used in operating activities	$ (88,012)	$ (73,117)
Net cash used in investing activities	108,038	(286,988)
Net cash provided by financing activities	2,582	156,128
Effect of exchange rate changes on cash	(485)	922
Net increase in cash, cash equivalents, and restricted cash	$ 22,123	$ (203,055)

Operating activities

During the six months ended June 30, 2020, operating activities used $88.0 million of cash, primarily resulting from our net loss of $98.1 million. Cash usage from changes in our operating assets and liabilities was $18.4 million, which was primarily driven by an increase in our research and development tax credit receivable of $6.0 million and a decline in accounts payable and accrued expenses of $9.6 million. The decline in accounts payable and accrued expenses is primarily attributable to the payout of our annual bonuses consisting of $9.0 million in the first quarter of 2020. Non-cash adjustments to operating activities of $28.5 million was primarily due to $15.6 million in non-cash share-based compensation expense, and $5.6 million in non-cash impairment charges associated with our restructuring, offset by $2.0 million in amortization of the Strimvelis loss provision as an offset to research and development expense. Further, there were other non-cash adjustments, including unrealized foreign currency transaction losses on intercompany accounts by our U.K. subsidiary, of $7.0 million that were driven by foreign currency revaluation.

During the six months ended June 30, 2019, operating activities used $73.1 million of cash, resulting from our net loss of $81.3 million. Cash usage from changes in our operating assets and liabilities was $1.2 million, and net non-cash charges was $9.3 million. Our net loss was primarily attributable to research and development activities related to our developmental stage programs, discovery and pre-clinical costs, a $17.2 million in-process research and development charge associated with upfront and milestone payments relating to OTL-203 program for MPS-I, and our selling, general, and administrative expenses. Changes in operating assets and liabilities during the six months ended June 30, 2019 of $1.2 million is attributable to a $9.9 million increase in our research and development tax credit receivable, offset by a $0.4 million decrease in trade receivables, and $1.1 million decrease in prepaid expenses, other current assets, and other assets. This was offset by an increase in accounts payable, accrued expenses, and other long-term liabilities of $6.8 million. Included within our net loss is $9.3 million in net non-cash expenses and offsets to research and development expense, including $8.5 million in non-cash share-based compensation expense, $2.6 million in non-cash offsets to research and development expense associated with the amortization of our Strimvelis loss provision liability, $0.8 million in non-cash depreciation expense, and $2.9 million in other non-cash adjustments, including unrealized foreign currency transaction losses on intercompany accounts by our U.K. subsidiary of that were driven by foreign currency revaluation.

Investing activities

During the six months ended June 30, 2020 and 2019, we generated $108.0 million and used $287.0 million, respectively, of cash in investing activities. The increase in cash generated from investing activities in the six months ended June 30, 2020 compared to 2019 is attributable to maturities and sales of marketable debt securities of $168.1 million. This was offset by a $10.0 million deposit into a construction escrow account, of which we have taken in receipts of $1.9 million associated with qualified construction expenditure. In the six months ended June 30, 2020 and 2019, investing activities used $49.4 million and $287.0 million for the purchase of highly-rated, short duration marketable debt securities.

Financing activities

For the six months ended June 30, 2020 and 2019, cash provided by financing activities was $2.6 million and $156.1 million, respectively. In the six months ended June 30, 2020, we have had $2.6 million in proceeds related to share plan activity. In the six months ended June 30, 2019 we had proceeds from our follow-on offering of $130.2 million, net of underwriting discounts and issuance costs paid as of June 30, 2019, and proceeds from the issuance of our term loan of $24.7 million, net of debt issuance costs paid as of June 30, 2019. Additionally, we had proceeds of $1.3 million from the exercise of share options and issuance of ordinary shares as part of our ESPP in the six months ended June 30, 2019.

Funding requirements

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

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

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

We believe our existing cash, will enable us to fund our operating expenses and capital expenditure requirements into 2022. 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 Sated, or GAAP. The preparation of our financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that of our critical accounting policies which are described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Significant Judgments and Estimates" in our Annual Report, the following accounting policies involve the most judgment and complexity:

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

Accordingly, we believe the policies set forth above are critical to fully understanding and evaluating our financial condition and results of operations. If actual results or events differ materially from the estimates, judgments and assumptions used by us in applying these policies, our reported financial condition and results of operations could be materially affected. There have been no material changes to our critical accounting policies since December 31, 2019.

Off-balance sheet arrangements.

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

Tabular disclosure of contractual obligations.

During the six months ended June 30, 2020, there have been no material changes to our contractual obligations and commitments outside the ordinary course of business from those described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Contractual Obligations and Commitments" in our Annual Report for the year ended December 31, 2019, except as noted below:

- In April 2020, we amended our agreement with Oxford BioMedica. Upon amendment of the agreement, a milestone was deemed to have been met upon execution of the amended agreement, and we became obligated to issue 75,413 ordinary shares to Oxford BioMedica. The shares were issued to Oxford BioMedica in April 2020, and the expense associated with the milestone will be recorded in April 2020. We may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica agreement.

- On July 2, 2020 (the "Effective Date"), we entered into a manufacturing and technology development master agreement (the "Agreement") with MolMed S.p.A. ("MolMed"), pursuant to which MolMed will develop, manufacture and supply certain viral vectors and conduct cell processing activities for certain Orchard development and commercial programs. Under the terms of the Agreement, we are obligated to pay MolMed a minimum product manufacturing commitment of €2.7 million per annum for the term of the Agreement, which may increase to the mid-seven figures per annum upon the achievement of certain milestones that may require additional manufacturing capacity. Additionally, we have committed €10.4 million per annum for dedicated manufacturing and development resources, including exclusive manufacturing suites within MolMed's existing facilities, which we may increase or decrease on a rolling basis with between six and 12-months' prior written notice to MolMed. The Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The Agreement may be extended for an additional two years by mutual agreement of us and MolMed. We have the right to terminate the Agreement at its discretion upon 12-month's prior written notice to MolMed, and beginning no earlier than July 2, 2022, MolMed has the right to terminate the Agreement at its discretion upon 24-month's prior written notice to us. Each party may terminate the Agreement upon prior notice to the other party for an uncured material breach that the breaching party does not cure within the notice period.

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate sensitivity

As of June 30, 2020, we had cash, cash equivalents, marketable securities, and restricted cash of $232.9 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We have borrowed $25.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 6% plus LIBOR. As of June 30, 2020, the carrying value of the term loans under the credit facility was $24.9 million.

Foreign currency exchange risk

The Company is exposed to foreign currency exchange risk because it currently operates in the United Kingdom and the United States. The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the ultimate parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises finance and expends cash in U.S. dollars, and expects to continue to do so in the future. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency of the relevant entity at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net income (loss) for the respective periods. We recorded an unrealized foreign currency loss of $7.4 million and $1.9 million for the six months ended June 30, 2020, and 2019, respectively. These foreign currency transaction gains are primarily related to revaluation of intercompany balances denominated in currencies other than the U.S. dollar. The losses are included in other expense (income) in our consolidated statements of operations and comprehensive loss.

Assets and liabilities have been translated at the exchange rates at the balance sheet dates, while revenue and expenses are translated at the average exchange rates over the reporting period and shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net income (loss) but are included in our foreign exchange adjustment to other comprehensive loss, a component of shareholders' equity.

We do not currently engage in currency hedging activities in order to reduce our currency exposure, but we may begin to do so in the future. Instruments that may be used to hedge future risks include foreign currency forward and swap contracts. These instruments may be used to selectively manage risks, but there can be no assurance that we will be fully protected against material foreign currency fluctuations.

LIBOR Reform

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

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.

Based on this evaluation, 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 June 30, 2020, our disclosure controls and procedures were effective at the reasonable assurance level.

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

Changes in Internal Control Over Financial Reporting

During the three months ended June 30, 2020, there have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) or 15d-15(f) 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 June 30, 2020, 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 Quarterly Report and in our other SEC filings. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and/or prospects. This Quarterly Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in these forward-looking statements, as a result of certain factors including the risks described below and elsewhere in this Quarterly Report and our other SEC filings. See "Special Note Regarding Forward-Looking Statements" above.

Risks related to our financial position and need for additional capital

We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred net losses. We historically have financed our operations primarily through private placements of our convertible preferred shares and through sales of our ADSs in our initial public offering and follow-on offering. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union, building a global commercial infrastructure to support anticipated commercialization of our product candidates, including OTL-200 for metachromatic leukodystrophy, or MLD, and OTL-103 for Wiskott Aldrich syndrome, or WAS, if such product candidates are approved, as well as expanding our team. To date, Strimvelis is our only commercialized product, and absent the realization of sufficient revenues from product sales of Strimvelis in addition to our current or future product candidates, if approved, we may never attain profitability. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially over time if, and as, we:

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

- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality, regulatory affairs, process development and control, manufacturing, supply chain, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- encounter delays or setbacks in the preclinical testing, enrollment or conduct of our clinical trials for our product candidates, encounter delays in regulatory review timelines, such as for our MAA under review by the EMA, or experience high levels of absenteeism, due to the COVID-19 pandemic;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

Strimvelis is our only product that has been approved for sale and, to date, it has only been approved in the European Union for the treatment of ADA-SCID. Since receiving marketing authorization, only a limited number of patients have been treated with Strimvelis. Our revenue from sales of Strimvelis alone will not be sufficient for us to become profitable. Under the terms of our asset purchase and license agreement with GSK, or the GSK Agreement, we are required to use our best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, is commercially available for patients, and at all times at the San Raffaele Hospital in Milan, Italy, provided that a minimum number of patients continue to be treated at this site. To become and remain profitable, we must develop and eventually commercialize product candidates with greater market potential. This will require us to be successful in a range of challenging activities, and our expenses will increase substantially as we seek to complete necessary preclinical studies and clinical trials of our product candidates, and manufacture, market and sell these or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

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

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully develop and commercialize products. Although we generate revenue from the sale of Strimvelis, we do not expect to achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. For example, in connection with the GSK Agreement, we recorded a liability for Strimvelis representing the fair value of the future expected costs to maintain the marketing authorization in excess of expected future sales. Our ability to generate future revenues from product sales depends heavily on our and or our collaborators' success in:

- completing research and preclinical development of our product candidates and identifying attractive new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates, including maintaining or reaching target enrollment levels and collecting the necessary follow-up data during the COVID-19 pandemic;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related regulatory compliance for Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Strimvelis and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;

- implementing additional internal systems and infrastructure, as needed, including robust quality systems and manufacturing capabilities;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

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

We will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

Our operations have consumed a substantial amount of cash since our inception, and we recorded negative cash flows from operating activities in 2019 and the first six months of 2020, primarily due to our net loss of $163.4 million and $98.1 million, respectively. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the expansion of our commercial infrastructure in support of Strimvelis and our anticipated commercialization of OTL-200 for MLD and OTL-103 for WAS, if such product candidates are approved, continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and continue to enhance and optimize our vector technology and manufacturing processes. In addition, we expect to incur significant expenses related to product sales, post-marketing regulatory commitments, medical affairs, marketing, manufacturing, distribution and quality systems to support Strimvelis and any other products for which we obtain marketing approval. Furthermore, we will continue to incur additional costs associated with operating as a public company, including with respect to the system and process evaluations and testing of our internal controls and financial reporting, and our independent auditor's attestation report on our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on reasonable terms, or at all, we would be forced to delay, reduce or eliminate certain of our research and development programs and/or commercialization efforts.

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

- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities required, including quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution, to support Strimvelis in the European Union and any other products for which we obtain marketing approval;
- qualifying for, and maintaining adequate coverage and reimbursement by, government and payors on a timely basis for Strimvelis and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our product candidates or future product candidates, including the need to conduct long-term follow-up for up to 15 years for our development programs and additional clinical trials to support marketing approvals for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs, including our ability to resolve delays in trial enrollment as a result of the COVID-19 pandemic;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Strimvelis and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;

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

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

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

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

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

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

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

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

We have concentrated our research and development efforts on our autologous *ex vivo* gene therapy approach, and our future success depends on our successful development of commercially viable gene therapy products. There can be no assurance that we will not experience problems or delays in developing new products and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. Although we have established a commercial infrastructure for the production of Strimvelis in the European Union and we are building a global commercial infrastructure to support commercialization of OTL-200 for MLD and OTL-103 for WAS, if such product candidates are approved, we may experience delays in establishing a sustainable, reproducible and scalable manufacturing capability with commercial CDMO partners, which may prevent us from commercializing our product candidates for which we obtain marketing approval on a timely or profitable basis, if at all.

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

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

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

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

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

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

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

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

There have been several adverse events and serious adverse events, or SAEs, attributed to gene therapy treatments in the past, including reported cases of leukemia with the use of gammaretrovirus vector and death seen in other clinical trials. Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. Possible adverse side effects and adverse events that may occur with treatment with gene therapy products include an immunologic reaction early after administration that could substantially limit the effectiveness of the treatment or represent safety risks for patients. Another traditional safety concern for gene therapies using viral vectors has been the possibility of insertional mutagenesis by the vectors, leading to malignant transformation of transduced cells. While our gene therapy approach is designed to avoid immunogenicity after administration, there can be no assurance that patients would not develop antibodies that may impair treatment. Our approach involves the use of integrating vectors which have the potential for genomic disruption and therefore could interfere with other genes with adverse clinical effects. If any of our gene therapy product candidates demonstrates adverse side effects or adverse events at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

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

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

- regulatory authorities may suspend or withdraw approvals of such product or product candidate;
- regulatory authorities may require additional warnings or limitations of use in product labeling;

- we may be required to change the way a product candidate is distributed, dispensed, or administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

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

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

We have limited experience conducting company-sponsored clinical trials and to date most of our product candidates have been evaluated under investigator-sponsored clinical trials using drug product manufactured at the applicable or relevant academic site. We did not control the design or administration of these investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these clinical trials. Investigator-sponsored clinical trials are often conducted under less rigorous clinical and manufacturing standards than those used in company-sponsored clinical trials. For example, the drug product used in our company-sponsored clinical trials is manufactured by third party 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 GOSH, one patient experienced an SAE, staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. A similar SAE, bacteremia, was observed in the clinical trial conducted at UCLA for OTL-101 with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. The bacteremia resolved on Day 3 without sequelae. We believe that our commercial manufacturing processes for 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.

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

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

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

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

For example, although sustained clinical activity has been observed in clinical trials to date for OTL-200 for MLD and OTL-103 for WAS, follow-up in each of these clinical trials is ongoing and there can be no assurance that the results, in each case as of the applicable primary endpoint measurement date, seen in clinical trials of any of our product candidates ultimately will result in success in clinical trials or provide adequate support for marketing approvals without conducting further clinical trials. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical trials, and may not be repeated or observed in ongoing or future trials involving our product candidates. There is limited data concerning long-term safety and efficacy following treatment with our product candidates. For example, OTL-202 for mucopolysaccharidosis type III-B, or MPS-IIIB, has not yet been tested in humans, and we recently dosed our first patient in a proof-of-concept investigational study of OTL-201 for MPS-IIIA. These and any of our other product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in preclinical studies. Our product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical trials. There can be no assurance that any of these trials will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates. In addition, there can be no assurance that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.

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

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

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

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

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. Additionally, the recent COVID-19 global pandemic has had and may continue to have a sustained impact on our ability to recruit and follow-up with patients either due to continued or renewed restrictions on travel or shelter-in-place orders or policies, or due to changes in patient willingness to participate in trials or travel to study sites in the wake of the pandemic. Additionally, COVID-19 related study site policies may create delays or setbacks in our ability to continue to enroll or to dose patients. For example, the enrollment timeline for OTL-201 was initially delayed by three months, and we may face delays in the future due to the impacts of the COVID-19 pandemic. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results from our clinical trials for OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates. Before we submit our product candidates for marketing approval, the FDA and/or the EMA may require us to conduct additional clinical trials, or evaluate patients for an additional follow-up period.

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

The FDA generally finds trials using historical controls to be credible only when the observed effect is large in comparison to variability in disease course. Due to the nature of the indications our product candidates are designed to treat, and the limited number of patients with these conditions, a placebo-controlled and blinded study is not practicable for ethical and other reasons. It is possible the FDA will not consider our comparisons to natural history data and, where available, historical transplant data or intra-subject comparison between before gene therapy and after gene therapy, to provide clinically meaningful results. Additionally, even though OTL-200 for MLD and OTL-103 for WAS have achieved the primary endpoints in their respective ongoing registrational clinical trials, neither the FDA nor EMA has yet approved the clinical meaningfulness of the trial results and their sufficiency to support a marketing authorization.

For example, the FDA recently provided written feedback on the sufficiency of our data package for OTL-200, including the clinical endpoints, natural history analysis and chemistry and manufacturing and controls, or CMC, data. We intend to use the FDA's guidance to further analyze the latest available CMC and clinical data for OTL-200, file an IND application and seek Regenerative Medicine Advanced Therapy, or RMAT, designation in 2020 in an effort to resolve open matters before the intended BLA submission, although there can be no guarantee we will be successful in resolving such matters. It is possible that the FDA may recommend or require us to conduct further studies or analyses with respect to our product candidates or that the EMA may recommend or require us to conduct additional registrational trials for our product candidates, possibly involving a larger sample size or a different clinical trial design, particularly if the EMA does not find the results from a previous trial to be sufficiently persuasive to support a MAA submission. The FDA or EMA may also require that we conduct a longer follow-up period of patients treated with our product candidates prior to accepting a BLA or MAA submission, as applicable.

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

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

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

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

To date, most of the clinical trials conducted on our product candidates have been conducted outside the United States. For example, we do not yet have an IND open in the United States for OTL-200 for MLD, OTL-203 for MPS-I or OTL-300 for TDT. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA, as noted in the risk factor immediately above. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, due to study design or otherwise, it would likely result in the need for additional trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates. Further, without an IND open in the United States, we forego more frequent interactions and dialogue with FDA regarding the design and conduct of our trials as well as product comparability, which may delay or halt the development of our product candidates later in development should FDA later disagree with the design or conduct of our trials or product comparability approach.

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

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

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

In those cases where clinical trials were conducted using vector and/or drug product manufactured at academic research centers (e.g., OTL-101 for the treatment of ADA-SCID), we will need to demonstrate comparability between vector and drug product manufactured by our CDMOs with vector and/or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another and in some cases we may elect to initially seek approval of our product candidate using one cellular source only, and subsequently seek approval for the use of the other cellular source. We cannot be assured that the FDA, EMA or other regulatory authority will not require us to conduct additional analytical comparability analyses, preclinical studies and/or clinical trials before approving our product candidates using these production methods and processes. Moreover, we cannot be assured that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval or our product candidates using these production methods and processes. For example, both the FDA and the EMA have advised us that they will require clinical data using drug product that has been cryopreserved as part of our planned BLA and MAA submissions for OTL-103 for WAS.

If the FDA, EMA or other regulatory authority does not accept our comparability data or if an adequate potency assay for a product candidate is not available or supported by such regulatory authority, our regulatory approval for such product candidate, if any, will be limited or delayed. For example, if one or more of these regulatory authorities does not accept that our cryopreservation process produces a product candidate that is comparable to our fresh drug product, our regulatory approval, if any, would be limited to our fresh product candidate until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials or require additional test method development. Potency assays that measure strength (e.g., enzymatic activity, or other relevant function) of each active ingredient are required for release testing of licensed biological drug products, comparability and stability analysis. In certain conditions, such as MLD and ADA-SCID, the potency of a product candidate may be readily measured through enzymatic activity; however, for an intracellular protein such as WAS, such an assay is not so readily available. We are therefore working with the FDA and EMA to identify a relevant function by which potency can be measured for OTL-103 for the treatment of WAS. If an adequate potency assay for a product candidate, such as OTL-103, is not available, or if the FDA, EMA or other regulatory authority require additional tests or recommend a different approach to support the potency of any of our product candidates, regulatory approval for any such product candidates, if any, will be delayed, and such regulators might request additional clinical data to support comparability analysis. Similarly, if one or more of these regulatory authorities does not accept that our drug product manufactured with HSCs derived from the patient's mobilized peripheral blood is comparable to drug product manufactured with HSCs derived from the patient's bone marrow, any regulatory approval would be limited to drug product manufactured with HSCs derived from the patient's bone marrow until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials. In April 2020, the FDA advised us that we may need to generate additional data to demonstrate the comparability of our OTL-200 drug product derived from the patient's mobilized peripheral blood and the OTL-200 drug product derived from the patient's bone marrow, and that the data provided to date are inadequate to determine if the two materials are comparable. Further, the FDA requested that we provide data that demonstrates the comparability of the different OTL-200 product formulations used across our trials. Failure to demonstrate such comparability, or if we are required to conduct additional testing or additional clinical trials, potentially at additional sites, would delay any marketing authorization and adversely affect the commercial viability of our product candidates and may adversely affect our ability to generate revenue, as a result of which our business, prospects, financial condition and results of operations may suffer.

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

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

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

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

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

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

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

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

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

The FDA and comparable other regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. OTL-101 for ADA-SCID has received a Breakthrough Therapy designation from the FDA, OTL-103 for WAS received RMAT designation from the FDA and OTL-300 received a Priority Medicines, or PRIME, designation from EMA. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

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

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

In addition, the FDA has granted Rare Pediatric Disease designation to Strimvelis, OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS, OTL-201 for MPS-IIIA and OTL-203 for MPS-I, 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 until September 30, 2020, with potential for PRVs to be granted until 2022. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for OTL-101 for ADA-SCID OTL-200 for MLD, OTL-103 for WAS, OTL-201 for MPS-IIIA and OTL-203 for MPS-I and qualify for such a PRV, the program may no longer be in effect at the time or the value of any such PRV may decrease such that we are may not be able to realize the benefits of such PRV.

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

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

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

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

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

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

We have sought and received orphan drug designation for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-IIIA from the FDA and EMA, for OTL-203 for MPS-I from the FDA, and for OTL-300 for TDT from the EMA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not mean that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

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

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

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

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

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by the EMA or other regulatory authorities in other countries or jurisdictions, and approval by the EMA or another regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit an MAA to the EMA for approval of our product candidates in the European Union but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

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

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the European Union took effect on January 31, 2020 (the "Exit Day"). Brexit could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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

As part of its marketing authorization process, the EMA may grant marketing authorizations for certain categories of medicinal products on the basis of less complete data than is normally required, when doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the Committee for Medicinal Products for Human Use, or CHMP, to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating or life-threatening diseases and those designated as orphan medicinal products.

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

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

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

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

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

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

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

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance cGMP requirements and adherence to commitments made in the BLA or foreign marketing application. In response to the COVID-19 pandemic, on March 10, 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities and products while local, national and international conditions warrant. On March 18, 2020, the FDA announced its intention to temporarily postpone routine surveillance inspections of domestic manufacturing facilities and provided guidance regarding the conduct of clinical trials which the FDA continues to update. As of June 23, 2020, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to maintain this pace and delays or setbacks are possible in the future. On July 10, 2020, the FDA announced its goal of restarting domestic on-site inspections in July but such activities will depend on data about the virus' trajectory in a given state and locality and the rules and guidelines that are put in place by state and local governments. The FDA has developed a rating system to assist in determining when and where it is safest to conduct prioritized domestic inspections. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

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

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

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

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

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

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

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

We operate in a highly competitive segment of the biopharmaceutical market. We face competition from many different sources, including larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies, some of which are being marketed by large and international companies. In addition, we expect to compete with new treatments that are under development or may be advanced into the clinic by our competitors. There are a variety of product candidates, including gene therapies, in development for the indications that we are targeting, 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, our commercial product Strimvelis and our product candidates. We do not have any issued patents covering our commercial product Strimvelis or our product candidates, and only one patent family with patent applications pending in the United States and Europe with patent claims directed to our OTL-101 product candidate and its use in the treatment of ADA-SCID. This means that barriers to entry that typically apply in the case of pharmaceutical and biopharmaceutical companies with issued patents covering aspects of their proprietary technologies, products and product candidates, such as composition of matter claims, will generally not apply to our commercial product or our product candidates, and this may expose us to competition from other biopharmaceutical companies, particularly those companies that possess greater financial resources and more mature product candidate development, manufacturing, marketing and distribution resources than we do. Although our product candidates, if approved, may be eligible for marketing and/or data exclusivities in, for example, the United States and Europe, these exclusivities would not prevent another biopharmaceutical company from conducting its own clinical trials to develop and seek regulatory approval of a competitive product. We are not the only company that is developing and commercializing products using a lentiviral-based autologous *ex vivo* gene therapy approach, and these competitive approaches may be comparable or superior to our approach. One or more of these companies may seek to develop products that compete directly with our commercial product or one or more of our product candidates, the result of which could have a material adverse effect on our business. In addition, many universities and private and public research institutes are active in our target disease areas.

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

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

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

As part of our strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates. We may spend several years completing our development of any particular current or future product candidates, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. For example, in May 2020, we announced our decision to reduce investment in the development of OTL-101 for ADA-SCID and OTL-300 for TDT and to focus on other product candidates in our pipeline and new research and development efforts in less rare diseases. Our focus on the advancement of our other product candidates may ultimately prove to be unsuccessful or less successful than if we had continued to prioritize OTL-101 or OTL-300, and if we choose to reprioritize OTL-101 or OTL-300 in the future, we may experience delays that would not have otherwise occurred, due to inefficiencies from loss of organizational knowledge and ramp up costs. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

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

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

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

Risks related to manufacturing and supply

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial product or our product candidates or otherwise harm our business.

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

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

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

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

Before we can begin to commercially manufacture our viral vector or product candidates in a CDMO facility, we must obtain regulatory approval from the FDA for our manufacturing processes and for the facility in which manufacturing is performed. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product and, therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our CDMOs manufacturing facility by the FDA and other relevant regulatory authorities before any of our gene therapy product candidates can obtain marketing approval. In order to obtain approval, we will need to ensure that all of our processes, quality systems, methods, equipment, policies and procedures are compliant with cGMP, and perform extensive audits of vendors, contract laboratories, CDMOs and suppliers. If any of our vendors, contract laboratories, CDMOs or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to spend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks related to our reliance on third parties

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

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

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

We may enter into additional collaborations with third parties in the future. Any collaborations we enter into in the future may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- we may not achieve any milestones, or receive any payments, under our collaborations, including milestones and/or payments that we expect to achieve or receive;
- the clinical trials conducted as part of these collaborations may not be successful;

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

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

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing shareholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of several factors. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks related to commercialization of our product candidates

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

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

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

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

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

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

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

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

If the size and value of the market opportunities for our product candidates are smaller than our estimates, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for primary immune deficiencies, inherited metabolic and neurodegenerative genetic disorders and rare inherited blood disorders. Additionally, we plan to focus research and development projects on less rare indications, including two new research programs. 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 OTL-200 for MLD we are now initially focused primarily on annual incidence of the disease, and in the case of OTL-103 for WAS we are initially focused primarily on prevalence of the disease. In each case this means the initial market opportunity for these product candidates may be smaller than the total addressable market opportunity that could be achieved over time. Moreover, we recently decided to reduce our investment in two of our product candidates, OTL-101 for ADA-SCID and OTL-300 for TDT. If we are unable to advance other product candidates with attractive market opportunities, our future product revenues may be smaller than anticipated and our business may suffer. Patient identification efforts also influence the ability to address a patient population. If efforts in patient identification are unsuccessful or less impactful than anticipated, we may not address the entirety of the opportunity we are seeking. As a result, the number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

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

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

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

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

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

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve market approval. In the United States and markets in other countries, patients generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments, such as stem cell transplants. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be covered and paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other payors. If coverage and adequate reimbursement 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. 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. Further, due to the COVID-19 pandemic, millions of individuals have lost or will be losing employer-based insurance coverage, which may adversely affect our ability to commercialize our products.

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

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

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

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

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

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

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

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

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, includes a provision that decreased the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, commonly referred to as the “individual mandate,” to $0, effective January 1, 2019. On December 14, 2018, a federal district court in Texas ruled the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional, and remanded the case to the lower court to reconsider its earlier invalidation of the full ACA. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case, and has allotted one hour for oral arguments, which are expected to occur in the fall. Pending review, the ACA remains in effect, but it is unclear at this time what effect the latest ruling will have on the status of the ACA.

Further, since January 2017, President Trump signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. The Trump administration concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until those appropriations are made. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payers who argued were owed to them. This decision was appealed to the U.S. Supreme Court, which on April 27, 2020, reversed the U.S. Court of Appeals for the Federal Circuit’s decision and remanded the case to the U.S. Court of Federal Claims, concluding the government has an obligation to pay these risk corridor payments under the relevant formula. The effects of this gap in reimbursement on third-party payers, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. In December 2018, the CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of the federal district court litigation regarding the method CMS uses to determine this risk adjustment. In addition, CMS published a final rule that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Congress may consider other legislation to replace elements of the ACA.

Additionally, in January 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device exercise tax on non-exempt medical devices. However, on December 20, 2019, President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future. Further, the BBA, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." Congress also could consider subsequent legislation to replace elements of the ACA that are repealed. Thus, the full impact of the ACA, any law replacing elements of it, and the political uncertainty surrounding any repeal or replacement legislation on our business remains unclear. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and will remain in effect through 2030 unless additional Congressional action is taken; however, pursuant to the CARES Act, these reductions will be suspended from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the U.S. government sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the Trump administration previously released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, or restrictions on certain product access, and marketing cost disclosure and transparency measures, which, in some cases, are designed to encourage importation from other countries and bulk purchasing.

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

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

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

Risks related to our business operations

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

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

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

We are developing our autologous *ex vivo* gene therapies to address rare diseases for which there are currently limited or no available therapeutic options. Media attention to individual patients' expanded access requests has resulted in the introduction and/or passage of legislation at the local and national level referred to as "Right to Try" laws which are intended to help enable patient access to unapproved therapies. Such legislation includes the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, which was signed into law on May 30, 2018. New and emerging legislation regarding expanded access to unapproved drugs for life-threatening illnesses could negatively impact our business in the future.

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

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

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

We are highly dependent on principal members of our executive team and key employees, including our 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.

In addition, changes in senior management may cause disruptions to our business. In March 2020, Mark Rothera stepped down as our President & Chief Executive Officer. Bobby Gaspar, M.D., Ph.D. was appointed as Chief Executive Officer, and Frank Thomas was appointed as President & Chief Operating Officer. If we are unable to manage an orderly transition in this case or for other key personnel in the future, our business may be adversely affected.

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

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

In May 2020, we undertook an organizational restructuring that reduced our workforce by approximately 25%, including the closure of our Menlo Park, California office. We also decided to discontinue building out our manufacturing facility in Fremont, California, despite having devoted costs and resources to the project, which may not be recouped, and despite incurring wind down costs associated with abandoning the construction. We have recorded $5.6 million in non-cash impairment charges associated with the Fremont operating lease right-of-use asset, design costs classified as construction-in-process, and laboratory equipment at our Menlo Park facility. If we are unable to sublease the facility and recover costs associated with servicing the lease, more impairment charges may be required. Effecting any restructuring places significant strains on management, our employees and our operational, financial and other resources. Furthermore, restructurings take time to fully implement and involve certain additional costs, including severance payments to terminated employees, and we may also incur liabilities from early termination or assignment of contracts, potential litigation or other effects from such restructuring. This restructuring, and the attrition that may occur following this reduction in force, may result in the loss of institutional knowledge and expertise and the reallocation and combination of certain roles and responsibilities across the Company, all of which could adversely affect our operations. Such effects from our restructuring program could have a material adverse effect on our ability to execute on our business plan. There can be no assurance that we will be successful in implementing our restructuring program. We may not realize, in full or in part, the anticipated benefits, savings and improvements in our cost structure from our restructuring efforts due to unforeseen difficulties, delays or unexpected costs. If we are unable to realize the expected operational efficiencies and cost savings from the restructuring, our operating results and financial condition would be adversely affected. Furthermore, we may incur unanticipated charges or make cash payments as a result of our restructuring initiative that were not previously contemplated which could result in an adverse effect on our business or results of operations. Our restructuring plan may also be disruptive to our operations. For example, our headcount reductions could yield unanticipated consequences, such as increased difficulties in implementing our business strategy, including retention of our remaining employees.

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

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

We acquired worldwide rights to Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDT in April 2018 pursuant to the GSK Agreement, and worldwide rights to OTL-203 for MPS-I in May 2019 pursuant to an exclusive licensing agreement with Telethon-OSR. The GSK Agreement significantly changed the composition of our operations, markets and product candidate mix, and we are continuing to adapt our organization to support these acquisitions. For example, in May 2020, we announced a reduction of the investment in and scope of our OTL-101 and OTL-300 programs and, based on the reallocation of capital, we have determined to prioritize other programs, including research and development projects in less rare indications. Our future success depends, in part, on our ability to continue to address these changes, and, where necessary, to attract and retain new personnel that possess the requisite skills called for by these changes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In the event we decide to conduct clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Economic Area, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR includes restrictions on cross-border data transfers. The GDPR may increase our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities. Further, the United Kingdom's vote in favor of exiting the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated now that the United Kingdom has left the EU.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

These developments, or the perception that any of them could occur, have had, and may continue to have, a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. As a result of Brexit, the EMA, formerly situated in London, relocated to Amsterdam. Following the Transition Period, there is a risk that the relocation will interrupt current administrative routines and occupy resources, which may generally adversely affect our dealings with the EMA. Further, there is considerable uncertainty resulting from a lack of precedent and the complexity of the United Kingdom and EU's intertwined legal regimes as to how Brexit (following the Transition Period) will impact the life sciences industry in Europe, including our company, including with respect to ongoing or future clinical trials. Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from EU directives and regulations, the withdrawal could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. The impact will largely depend on the model and means by which the United Kingdom's relationship with the European Union is governed post-Brexit. For example, following the Transition Period, the United Kingdom will no longer be covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products, including our product candidates, will be required in the United Kingdom, the potential process for which is currently unclear. As a result, we cannot predict the impact that Brexit will have on (i) the marketing of pharmaceutical products, (ii) the process to obtain regulatory approval in the United Kingdom for product candidates or (iii) the award of exclusivities that are normally part of the EU legal framework (for instance Supplementary Protection Certificates, Pediatric Extensions or Orphan exclusivity). Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom or the European Union and restrict our ability to generate revenue and achieve and sustain profitability.

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

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

As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our ADSs. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which European Union rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital.

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

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

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

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

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from European Union directives and regulations, Brexit, following the Transition Period, could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. For example, as a result of the uncertainty surrounding Brexit, the EMA relocated to Amsterdam from London. Following the Transition Period, the United Kingdom will no longer be covered by the centralized procedures for obtaining EU-wide marketing and manufacturing authorizations from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products will be required in the United Kingdom, the potential process for which is currently unclear. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom or the European Union and limit our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom or the European Union for our product candidates, or incur significant additional expenses to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the United Kingdom. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the European Union.

The uncertainty concerning the United Kingdom's legal, political and economic relationship with the European Union following Brexit may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise). It is possible that following the Transition Period the application of charges to stamp duty and stamp duty reserve tax to issues or transfers of our ordinary shares to depositary receipt systems or clearance services could be affected. Although under current law and Her Majesty's Revenue & Customs published practice it is not expected that any stamp duty or stamp duty reserve tax, or SDRT, would arise in respect of any issue or transfer of our ordinary shares into a clearance service or depositary receipt system where it forms an integral part of capital raising, it is possible that following the Transition Period, existing legislation (which is not presently enforceable and which the Government indicated in April 2017 would not be applied following Brexit) could be applied, for example in the event of a change in Government policy, such that stamp duty and/or SDRT would apply in respect of any issue or transfer of our ordinary shares occurring thereafter including in respect of an issue or transfer which is integral to the raising of capital. In this event, we may be expected to bear any such stamp duty or SDRT (which, based on the existing legislation would be charged, in effect, at the rate of 1.5% of the value of the ordinary shares so issued or transferred). Any such charge would therefore represent an additional cost of our seeking to raise additional capital through further issuances of our ordinary shares.

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

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

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

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

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

We are conducting clinical trials for our product candidates in the United States and Europe, which are currently being affected by the COVID-19 pandemic and will likely continue to be affected. While our clinical sites are currently still treating patients in trials for OTL-201, OTL-103 and OTL-200 (for the treatment of MPS-IIIA, WAS and MLD, respectively), these centers are also devoting significant resources to patients with COVID-19, which could limit their ability to enroll additional patients in ongoing clinical trials. Some factors from the COVID-19 pandemic that have delayed and may continue to delay or otherwise adversely affect enrollment in or the progress of our clinical trials for some or all of our product candidates, as well as our business generally, include:

- the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, hospitals or academic centers serving as our clinical trial sites and staff supporting the conduct of our clinical trials;
- limitations on travel that could interrupt treatment center qualification, key trial activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that may impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials;
- interruption in global shipping affecting the transport of clinical trial materials, such as patient samples, investigational drug product and conditioning drugs and other supplies used in our clinical trials;
- business disruptions caused by potential workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments and operations, disruptions or delays in subleasing any leased facilities no longer required for our business operations, staffing shortages, travel limitations or mass transit disruptions, any of which could adversely impact our business operations or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors;
- business disruptions involving our third parties on whom we rely, including CROs and other collaborators for the conduct of our clinical trials or our third-party suppliers or CDMOs, which could impact their ability to perform adequately or disrupt our supply chain; and
- changes in hospital or research institution policies or government regulations, which could delay or adversely impact our ability to conduct our clinical trials.

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

The extent and impact of such disruptions are currently unpredictable. Any prolongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development, study and regulatory submissions of our product candidates. While we are still preparing for a potential approval by the EMA in 2020 of OTL-200 for the treatment of MLD under an accelerated assessment, the timeline could be extended as a result of the coordination needed among us, the EMA, our clinical site, our manufacturing partners and other key stakeholders involved in the review process during this time. The COVID-19 global pandemic may also result in interruption or delays in the operations of the FDA and EMA and other regulatory agencies, which could further delay our anticipated regulatory submissions and any potential approval of our product candidates.

In addition, the COVID-19 pandemic has impacted our ability to generate revenue from the sale of Strimvelis. Ospedale San Raffaele, Milan, Italy, the treatment site for Strimvelis, postponed scheduling and treating non-urgent patients with the therapy for several months, though was able to resume such treatments in June 2020. Although we derive limited revenue from sales of Strimvelis, a prolonged postponement of treatments would significantly reduce our sole source of product revenue.

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

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

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

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

We currently have $25.0 million of principal indebtedness outstanding under our senior term facilities agreement dated as of May 24, 2019, as amended April 7, 2020, between us, as borrower, and MidCap Financial (Ireland) Limited, as lender, or the Credit Facility. We have the ability to borrow up to an additional $50.0 million in the future under the Credit Facility upon satisfaction of certain conditions. Our existing indebtedness and any additional indebtedness we may incur could require us to divert funds identified for other purposes for debt service and impair our liquidity position.

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

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

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

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

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

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

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

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

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

Despite our security measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The ongoing COVID-19 pandemic and the related disruptions to our business and our collaborators’, contractors’ and consultants’ businesses may increase the risk of cyberattacks. If any cyberattack or data breach were to occur in the future and cause interruptions in our or our collaborators’, contractors’ or consultants’ operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Risks related to our intellectual property

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

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

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

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

In the event that a holder of any such patents seeks to enforce its patent rights against us with respect to one or more of our products or product candidates, and our defenses against the infringement of such patent rights are unsuccessful, we may be precluded from commercializing such products and product candidates, even if approved, without first obtaining a license to some or all of these patents, which may not be available on commercially reasonable terms or at all. Moreover, we may be required to pay significant fees and royalties to secure a license to the applicable patents. Such a license may only be non-exclusive, in which case our ability to stop others from using or commercializing technology and products similar or identical to ours may be limited. Furthermore, we could be liable for damages to the holders of these patents, which may be significant and could include treble damages if we are found to have willfully infringed such patents. In the event that a challenge to these patents were to be unsuccessful or we were to become subject to litigation or unable to obtain a license on commercially reasonable terms with respect to these patents, it could harm our business, financial condition, results of operations and prospects.

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

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

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

We are highly dependent on the intellectual property and data licensed to us by third parties that are important or necessary to the development of our technology and products and product candidates, including technology related to the manufacture and use of our products and product candidates. In particular, we do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis or any of our lead product candidates. We have in-licensed one U.S. patent application and a counterpart European patent application, know-how and data from UCLA and UCL Business plc, or UCLB, relating to OTL-101 for ADA-SCID. In addition, we have in-licensed certain know-how and data from GSK and Telethon-OSR, relating to Strimvelis, OTL-103 for WAS, OTL-200 for MLD, and OTL-300 for TDT, and certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-I. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

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

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

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

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

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. We currently do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis, OTL-200 or OTL-103. Many of our products and product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all. Our or our licensors' failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties, in particular, other established and better financed gene therapy companies having established development, manufacturing and distribution capabilities, to make competing products or impact our ability to develop, manufacture and market our products and product candidates, even if approved, on a commercially viable basis, if at all, which could have a material adverse effect on our business.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Some of the intellectual property rights we have licensed , including rights licensed to us by UCLA relating to our OTL-101 product candidate for ADA-SCID, may have been generated through the use of U.S. government and California state funding and may therefore be subject to certain federal and state laws and regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future products and product candidates pursuant to the Bayh-Dole Act of 1980. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. With respect to state funding, specifically funding via the California Institute of Regenerative Medicine, or CIRM, the grantee has certain obligations and the state or CIRM has certain rights. For example, the grantee has an obligation to share intellectual property, including research results, generated by CIRM-funded research, for research use in California.

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

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

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

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

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

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

Certain claims of our in-licensed patent applications contain, and any future patents we may obtain may contain, claims that relate to specific recombinant DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties.

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

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

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

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

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

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

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

- the patents of others may have an adverse effect on our business;
- others, including one or more of our competitors, may reverse engineer or independently develop the know-how or data, including clinical data, that we rely on for a competitive advantage;
- others may be able to make gene therapy products that are similar to our products or product candidates but that are not covered by the claims of the patents that we license or may own or license in the future or by our other intellectual property rights;
- we, our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patents or pending patent applications that we license or may own or license in the future;
- we, our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own or license in the future will not lead to issued patents;

- issued patents that we hold rights to or may hold rights to in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- one or more of our products or product candidates may never be protected by patents;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- we or our licensors or collaborators may choose not to file a patent application for certain trade secrets or know-how, and a third party may subsequently file a patent application or obtain a patent covering such intellectual property.

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

Risks related to ownership of our securities

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

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

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

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

We could be subject to securities class action litigation.

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

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

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

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

Based upon our ordinary shares outstanding as of June 30, 2020, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 51% of our ordinary shares and ADSs. Depending on the level of attendance at our meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, the approval of certain significant corporate transactions and amendments to our Articles of Association. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that our shareholders may believe are in their best interest as shareholders. Some of these persons or entities may have interests that are different than those of our other shareholders. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs were sold in our initial public offering have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

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

Additional sales of our ADSs, or the perception that these sales could occur, could cause the market price of our ADSs to decline. If any of our large shareholders or members of our management team sell substantial amounts of ADSs in the public market, or the market perceives that such sales may occur, the market price of our ADSs and our ability to raise capital through an issue of equity securities in the future could be adversely affected. Additionally, we filed a registration statement with the SEC and may issue securities in one or more underwritten transactions, in "at-the-market" offerings or in other transactions from time to time. If we were to issue such securities in the public market, the trading price of our ADSs could decline. See "–A significant portion of our total outstanding ordinary shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our ADSs to drop significantly."

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

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

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

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

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

We are entitled to amend the deposit agreement and to change the rights of the ADS holders under the terms of such agreement, without the prior consent of the ADS holders. We and the depositary may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us or to the depositary. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depositary. In the event that the terms of an amendment are materially disadvantageous to ADS holders, ADS holders will only receive 30 days' advance notice of the amendment, and no prior consent of the ADS holders is required under the deposit agreement. Furthermore, we may decide to direct the depositary to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our ordinary shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility will terminate, ADS holders will receive at least 30 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but 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 United States Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs.

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

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

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

Except as described in this Quarterly Report and the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the 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 ADSs in the public market could occur at any time or the perception in the market that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. As of June 30, 2020, we have outstanding 97,497,739 ordinary shares. The holders of up to 24,699,842 shares of our ordinary shares are entitled to rights with respect to the registration of their ordinary shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these ordinary shares under the Securities Act would result in the ADSs representing them becoming freely tradable without restriction, except for ADSs purchased by affiliates. In addition, our directors, executive officers and other affiliates may establish, and certain executive officers, directors and affiliates have established, programmatic selling plans under Rule 10b5-1 of the Exchange Act, for the purpose of effecting sales of our ADSs. Generally, sales under such plans by our executive officers and directors require public filings. Any sales of securities by these shareholders, or the perception that those sales may occur, under such programmed selling plans, could have a material adverse effect on the trading price of our ADSs. In addition, 15.353,896 ordinary shares reserved for issuance upon the exercise of existing options outstanding and issuance of restricted stock as of June 30, 2020 under our current equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

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

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

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

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

As a result of the loss of our foreign private issuer status, we are now required to comply with the Exchange Act's domestic reporting regime, which will cause us to incur significant legal, accounting and other expenses.

As of June 28, 2019, we determined that we no longer qualify as a "foreign private issuer" as such term is defined in Rule 405 under the Securities Act, which means that we are required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. As of January 1, 2020, we have been required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We will have been required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. As a result of such compliance, we expect that the regulatory and compliance costs to us under U.S. securities laws will be higher than the cost we incurred as a foreign private issuer and therefore, we expect that the loss of foreign private issuer status will increase our legal and financial compliance costs and will make some activities highly time consuming and costly. We also expect that compliance with the rules and regulations applicable to U.S. domestic issuers will make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors. In addition, our officers and directors are no longer exempt from the reporting and "short-swing" profit recovery provisions of Section 16 of the Exchange Act and related rules with respect to their purchase and sales of our securities.

Because we are no longer an "emerging growth company," as defined in the JOBS Act, we must incur additional expenses and devote increased management time to compliance with additional disclosures that are applicable to companies that are not emerging growth companies.

From our initial public offering until December 31, 2019, we were an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). While we were an emerging growth company, we were permitted to take advantage of reduced regulatory and reporting requirements that are otherwise generally applicable to public companies. These included, without limitation, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding non-binding advisory votes on executive compensation and golden parachute payments. Because we ceased to be an emerging growth company effective as of December 31, 2019, we expect to incur additional expenses and to devote increased management time toward ensuring compliance with those requirements applicable to companies that are not emerging growth companies.

In particular, our independent registered public accounting firm is required to provide an annual attestation report, in compliance with Section 404 of the Sarbanes-Oxley Act, regarding the effectiveness of our internal control over financial reporting. See "–We will continue to incur increased costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management is required to devote substantial time to new compliance initiatives."

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

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

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. As a large-accelerated filer, we also require an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In order to achieve and maintain compliance with Section 404, we have documented and evaluated our internal control over financial reporting, which is both costly and challenging. In this regard, we continue to dedicate internal resources, have engaged outside consultants and adopted a detailed work plan to continually assess and document the adequacy of internal control over financial reporting, taken steps to improve control processes as appropriate, validated through testing that controls are functioning as documented and have implemented a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk in any given year that we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. Moreover, if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our 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.

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

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

We previously identified material weaknesses in our internal control over financial reporting. We may identify future material weaknesses in our internal control over financial reporting. If we are unable to remedy these material weaknesses, or if we fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our ADS price.

Our management previously identified deficiencies that were concluded to represent a material weakness in our internal control over financial reporting where we did not design or implement sufficient controls and other review procedures performed by personnel familiar with U.S. GAAP to evaluate the recognition and accrual of research and development related expenses and reimbursements. A material weakness is defined as a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected and corrected on a timely basis.

In response to the material weakness, we have enhanced our controls around the recognition and accrual of research and development related expenses and reimbursements, including:

- Hiring a third-party professional accounting consulting firm to assist in establishing and implementing appropriate financial reporting policies, processes and controls over the recognition and accrual of research and development related expenses and reimbursements;
- Documenting the step-by-step processes and controls necessary to ensure that the recognition and accrual of research and development related expenses and reimbursements are accounted for in accordance with U.S. GAAP;
- Enhancing documentation and controls supporting the recognition and accrual of research and development related expense and reimbursements; and
- Providing increased oversight and review of the accrual of research and development related expense and reimbursements by personnel familiar with U.S. GAAP.

These controls around our oversight and review of the accrual of research and development related expenses and reimbursements have operated for a sufficient period of time, and management's evaluation of such controls indicates that such controls are effective. Although we have determined that the previously identified material weakness has been remediated as of December 31, 2019, we cannot assure you that we will not identify other material weaknesses or deficiencies, which could negatively impact our results of operations in future periods.

More generally, if we are unable to meet the demands that have been placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, we may be unable to accurately report our financial results in future periods, or report them within the timeframes required by law or stock exchange regulations. Failure to comply with the Sarbanes-Oxley Act, when and as applicable, could also potentially subject us to sanctions or investigations by the SEC or other regulatory authorities. Any failure to maintain or implement required new or improved controls, or any difficulties we encounter in their implementation, could result in additional material weaknesses or significant deficiencies, cause us to fail to meet our reporting obligations or result in material misstatements in our financial statements. Furthermore, if we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed, and investors could lose confidence in our reported financial information. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

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

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

Comprehensive tax reform legislation could adversely affect our business and financial condition.

In December 2017, President Trump signed into law the Tax Cuts and Jobs Act of 2017, or TCJA, which makes significant changes to the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation and other changes that may impact our operations, in particular the operations of our wholly-owned U.S. subsidiary, Orchard Therapeutics North America.

In response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020, and the CARES Act was enacted on March 27, 2020. The CARES Act lifts certain deduction limitations originally imposed by the TCJA. Corporate taxpayers may carryback net operating losses (NOLs) originating during 2018 through 2020 for up to five years to recover taxes paid in prior years. The CARES Act also eliminates the 80% of taxable income limitations by allowing corporate entities to fully utilize NOL carryforwards to offset taxable income in 2018, 2019 or 2020. Taxpayers may generally deduct interest up to the sum of 50% of adjusted taxable income plus business interest income (30% limit under the TCJA) for tax years beginning January 1, 2019 and 2020. The CARES Act allows taxpayers with alternative minimum tax credits to claim a refund in 2020 for the entire amount of the credits instead of recovering the credits through refunds over a period of years, as originally enacted by the TCJA. In addition, the CARES Act raises the corporate charitable deduction limit to 25% of taxable income and makes qualified improvement property generally eligible for 15-year cost-recovery and 100% bonus depreciation.

Regulatory guidance under the TCJA, FFCR Act and the CARES Act is and continues to be forthcoming, and such guidance could have a material impact on our business and financial condition. It is likely that Congress will enact additional legislation in connection with the COVID-19 pandemic, some could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the TCJA, the FFCR or the CARES Act.

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

We operate through various subsidiaries in a number of countries throughout the world. Consequently, we are subject to tax laws, treaties, and regulations in the countries in which we operate, and these laws and treaties are subject to interpretation. We have taken, and will continue to take, tax positions based on our interpretation of such tax laws. Our transfer pricing arrangements are not generally binding on applicable tax authorities. The price charged for products, services, or the royalty rates and other amounts paid for intellectual property rights, could be challenged by the various tax authorities, resulting in additional tax liability, interest, and/or penalties. There can be no assurance that a taxing authority will not have a different interpretation of applicable law and assess us with additional taxes. If we are assessed with additional taxes, this may result in a material adverse effect on our results of operations and/or financial condition.

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

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

We believe that we were not a CFC in the 2019 taxable year, however, we may become a CFC in a subsequent taxable year. If we are classified as both a CFC and a passive foreign investment company, or PFIC (as discussed below), we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

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

Under the Code, we will be a PFIC, for any taxable year in which (1) 75% or more of our gross income consists of passive income or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. holder holds our shares, the U.S. holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

We do not believe that we were a PFIC in the 2019 taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by the spending of the cash we raise in any offering.

In certain circumstances, a U.S. holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a "qualified electing fund," or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute "marketable" securities under the Code), which each require the inclusion of a pro rata share of our income on a current basis. However, a U.S. holder may make a QEF election with respect to our ordinary shares or ADSs only if we agree to furnish such U.S. holder annually with required information, and we have not determined if we intend to prepare or provide the information that would enable U.S. holders to make a QEF election. However, a U.S. holder would be able to make a mark-to-market election with respect to our ordinary shares or ADSs as long as those shares or ADSs constitute marketable securities under the Code.

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

As a U.K. incorporated and tax resident entity, we are subject to U.K. corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any U.K. corporation tax. As of December 31, 2019, we had cumulative carryforward tax losses of $266.8 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to U.K. profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of U.K. taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

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

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

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

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

A change in accounting pronouncements or taxation rules or practices can have a significant effect on our reported results and may affect our reporting of transactions completed before the change is effective. New accounting pronouncements, taxation rules and varying interpretations of accounting pronouncements or taxation rules have occurred in the past and may occur in the future. The change to existing rules, future changes, if any, or the need for us to modify a current tax or accounting position may adversely affect our reported financial results or the way we conduct our business.

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

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

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

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

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

The principal differences include the following:

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

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

Sales of Unregistered Securities

Pursuant to the terms of our license and development agreement, as amended, with Oxford BioMedica (UK) Limited (“Oxford BioMedica”), on April 20, 2020 we issued 75,413 ordinary shares to Oxford BioMedica in connection with a milestone that was deemed to have been met on April 15, 2020. The offer, sale, and issuance of the shares is exempt from registration pursuant to Section 4(a)(2) of the Securities Act of 1933, as amended, as a transaction by an issuer not involving a public offering.

Item 3. Defaults Upon Senior Securities.

Not applicable.

Item 4. Mine Safety Disclosures.

Not applicable.

Item 5. Other Information.

None.

Item 6. Exhibits.

Exhibit Number	Description
10.1*†	Manufacturing and Technology Development Master Agreement, by and between Orchard Therapeutics (Europe) Limited, a wholly-owned subsidiary of the registrant, and MolMed S.p.A., dated July 2, 2020.
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.

† Portions of this exhibit have been omitted because they are both (i) not material and (ii) would likely cause competitive harm to the registrant if publicly disclosed.

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: August 6, 2020	By: /s/ Bobby Gaspar **Bobby Gaspar** Chief Executive Officer (Principal Executive Officer)
Date: August 6, 2020	By: /s/ Frank E. Thomas **Frank E. Thomas** President and Chief Operating Officer (Principal Financial Officer and Principal Accounting Officer)

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Exhibit 10.1

MANUFACTURING AND TECHNOLOGY DEVELOPMENT MASTER AGREEMENT

July 2nd, 2020

Between

Orchard Therapeutics (Europe) Limited

and

MolMed S.p.A.

THIS MANUFACTURING AND TECHNOLOGY DEVELOPMENT MASTER AGREEMENT (the "**Agreement"**) is entered into and made effective as of July 2nd, 2020 (the "**Effective Date**")

BY and **BETWEEN**:

(1) **Orchard Therapeutics (Europe) Limited**, with registered offices at 108 Cannon Street, London, EC4N 6EU, England, company number 09759506, (**OTL**); and

(2) **MolMed S.p.A.,** with registered offices at Via Olgettina 58, 20132 Milano, Italy, V.A.T. 11887610159, (**MolMed**).

Each of OTL and MolMed are referred to herein as a **Party** or, collectively, as **Parties**.

WHEREAS:

(A) On 11 April 2018, OTL entered into an asset purchase and license agreement (the **"GSK-OTL Agreement"**) with Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD (together, **"GSK-1"**), pursuant to which GSK-1 transferred to OTL its portfolio of approved and investigational rare disease gene therapies, including Strimvelis for Adenosine Deaminase Severe Combined Immune Deficiency ("**ADA-SCID**"), OTL-103 for Wiskott-Aldrich Syndrome ("**WAS**"), OTL-200 for Metachromatic Leukodystrophy ("**MLD**") and OTL-300 for Beta thalassemia ("**Beta Thal**");

(B) GlaxoSmithKline Intellectual Property Development Limited and GlaxoSmithKline Trading Services Limited (together **"GSK-2"**), and MolMed entered into a Strategic Manufacturing and Technology

Development Agreement on 19 March 2015, which was amended and restated on 1 September, 2016 (the "**Prior Agreement**") under which GSK reserved certain cell processing capacity at MolMed, and MolMed agreed to manufacture and supply certain viral vectors and to conduct certain cell processing development and commercial cell processing activities for GSK;

(C) On 11 April 2018, GSK-2 assigned the Prior Agreement to OTL and OTL assumed all rights and obligations of GSK-2 under the Prior Agreement;

(D) On 27 June 2019, OTL and MolMed entered into an amendment agreement through which [***].

(E) The Parties intend to carry out their collaboration by entering into this master agreement which sets forth the structure, rights, restrictions and obligations under which OTL desires and MolMed agrees to perform the Services.

IT IS HEREBY AGREED as follows:

1. DEFINITIONS AND INTERPRETATION

1.1 Definitions

As used in this Agreement, the following terms shall have the meanings set forth in this Clause 1.1 unless the context dictates otherwise:

Administrative Fee shall mean [***].

Affiliate means any Person, whether de jure or de facto, which directly or indirectly through one (1) or more intermediaries Controls, is Controlled by or is under common Control with that Person.

[***] shall mean [***].

[***] means [***].

Agreement has the meaning given in the Preamble.

AIFA means Agenzia Italiana del Farmaco (Italian Medicines Agency), or any successor entity thereto.

Applicable Law means all applicable federal, state, national and local laws, statutes or ordinances governing the provision of the Services or otherwise relevant to the performance of a Party's obligations under this Agreement, including any regulations, rules or published guidelines or pronouncements having the effect of law promulgated by any Regulatory Authority.

Approved Subcontractors means any Subcontractor i) selected by OTL and audited and qualified by MolMed and/or (ii) for which the Parties are not able to identify a viable alternative to perform such part of the Services. For the purpose of this Agreement shall be considered Approved Subcontractors the following entities: [***]

Arising General OTL IPR means any Arising OTL IPR that is not Arising Specific OTL IPR. For the avoidance of doubt, Arising General OTL IPR shall include any Arising OTL IPR that primarily relates to roller bottles, flasks, cell factories, plastic kits, plastic devices, bioreactors, equipment for vector and cell manipulation, process, analytical methods, quality assurance management, regulatory activities, which are used and/or applied for development, Manufacturing and control in the provision of the Services and which, in each case, do not relate specifically to the development or Manufacture of Products.

Arising OTL IPR means Arising General OTL IPR and Arising Specific OTL IPR that arises, is discovered, is invented or is developed, on the basis of OTL Information, through the performance of the Services or the performance of any other obligations under this Agreement.

Arising Specific OTL IPR means any Arising OTL IPR that relates specifically to the development or Manufacture of Products.

Availability Notice shall mean the notice provided by MolMed in writing to OTL, stating that the Deliverable is ready for delivery and collection.

Background Non-Enablement Know-How Notice has the meaning given in Clause 3.4(a).

Baseline Pricing Model means the model pursuant to which the new indication Manufacturing Fee shall be equal to [***].

Batch means the quantity of Product resulting from a single batch run.

Batch Certificate means the certification of the Batch signed by a Qualified Person pursuant to Clause 8

Breaching Party has the meaning assigned to such term in Clause 16(b) and 18.2 a).

Business Day means a calendar day (other than a Saturday or Sunday) on which banks are open for ordinary face to face business in London and Milan.

cGMP means the current good manufacturing practices with respect to the Manufacture of Products required by:

(a) if the Product is to be supplied to an ICH region, the relevant International Conference on Harmonisation Quality Guidelines relating to good manufacturing practice; and/or

(b) if the Manufacture is conducted within EEA or if the Product is to be supplied to a country within EEA, the standards, rules, principles and guidelines of Good Manufacturing Practices for medicinal products set out in Directive 2001/83/EC (as amended by Directive 2004/27/EC), Directive 2003/94/EC and EudraLex – Volume 4 of the Rules Governing Medicinal Products in the European Union entitled "*EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use*". and/or

(c) if the Manufacture is conducted within the United States of America or if the Product is to be supplied to a country within the United States of America, the standards, rules, principles and guidelines of the FDA for medicinal products.

Change of Control means, with respect to MolMed, that any Person [***] that did not previously have Control of MolMed assumes Control of MolMed.

Commercial Products shall mean Products for commercial use.

Commercial Specification shall mean the Specification for Commercial Product set forth in the Product Technical Specification.

Commercially Reasonable Endeavours means, with respect to a Party, such endeavours as are consistent with the endeavours and resources normally used by a Party in the exercise of its reasonable business discretion relating to either (a) a product owned by it or to which it has exclusive rights, which is of similar market potential at a similar stage in its development or product life, or (b) the provision of services; in each case taking into account issues of scientific risk, patent coverage, safety and efficacy, product profile, the competitiveness of the marketplace, the proprietary position of the compound or product, the regulatory structure involved, the profitability of the applicable products (including, without limitation, pricing and reimbursement status achieved), and other relevant factors, including without limitation, technical, legal, scientific and/or medical factors.

Confidential Information has the meaning assigned to such term in Clause 13.1.

Contract Year means the period commencing on the Effective Date and ending on 31st March (the **First Contract Year**); and (b) with respect to each subsequent Contract Year, the twelve (12) month period beginning on April 1st of each calendar year.

Control, Controls, Controlled or **Controlling** means:

(a) with respect to any Intellectual Property Right, Know-How, information or material, possession of the ability to grant the licences or sublicences as provided herein without violating the terms of any agreement or other arrangement with any Third Party (and a Party shall be deemed to Control certain specified Intellectual Property Right, Know-How, information or material to the extent of its individual or joint interest therein, as applicable); and

(b) with respect to any Person, [***] or any of its subsidiaries and/or affiliates:

(i) the holding (whether directly or through any controlled company, fiduciary company or nominee) of the majority of the voting rights with respect to that Person as exercisable in any relevant ordinary shareholders meeting; or

(ii) the holding (whether directly or through any controlled company, fiduciary company or nominee) of sufficient voting rights with respect to that Person to enable the exercise of a dominant influence over that Person in any relevant ordinary shareholders meeting; or

(iii) the holding of a dominant influence over that Person as a consequence of specific contractual obligations.

Critical Material means materials identified in **Schedule 5** used in the performance of the Service, purchased by MolMed but expressly requested by OTL.

Data means, in respect of any Human Biological Samples, information about such Human Biological Samples, such as pathology information and information regarding the integrity of Human Biological Samples. For the avoidance of doubt, Data does include personal identifiable information (meaning information which identifies a specific individual).

Data Processor Agreement means the Agreement to be signed between the Parties pursuant to which OTL appointed MolMed, in accordance with art. 28 of the GDPR as the data processor.

[***] shall mean [***].

Default Change of Control means any Change of Control of MolMed which either (a) is to an OTL Competitor or (b) in OTL's reasonable opinion creates a Material Business Risk for OTL.

Deliverable shall means the Products and the documents identified in **Schedule 7** as "deliverable".

Development Plan has the meaning given in **Schedule 3**.

Development Services has the meaning given to it in **Schedule 3.**

Disclosing Party has the meaning assigned to such term in Clause 13.1.

Drug Product Manufacturing Fees has the meaning given in **Schedule 2**.

Drug Product means the cell sample for transfer to the patient, following purification and transduction of the relevant Starting Cell Population as per the prescribed manufacturing process (which will typically involve transduction with the applicable Viral Vector for the relevant indication), and in each case as described in the relevant Specifications.

Effective Date has the meaning given in the Preamble.

EEA means European Economic Area.

EMA means the European Medicines Agency for the Evaluation of Medicinal Products of the European Union, or any successor agency thereto.

European Commission means the executive body of the European Union that has legal authority to grant marketing authorisation approvals for pharmaceutical products in the European Union following scientific evaluation and recommendation from the EMA or other applicable Regulatory Authorities.

European Union or **EU** means all countries that are officially recognised as member states of the European Union at any particular time during the Term.

EUTCD means the European Union Tissue and Cells Directive (Directive 2004/23/EC).

[***] Field means the research, development, manufacture and commercialisation of cell and gene therapy products based on ex vivo transduction of stem cell for palliation, diagnosis, cure or prevention of the [***] Indications and [***] Indications.

Exclusive Transduction Suite means each cell transduction manufacturing suite described in **Schedule 4**.

FDA means the U.S. Food and Drug Administration, or any successor entity thereto.

First Contract Year has the meaning given in the definition of "Contract Year".

First Party has the meaning given in Clause 18.2 (b).

Force Majeure Event has the meaning given in Clause 20.8

GSK-OTL Agreement means an asset purchase and license agreement between Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD (together, **"GSK-1"**), and OTL upon which GSK-1 transferred to OTL its portfolio of approved and investigational rare disease gene therapies.

Human Biological Samples means human biological samples (including any derivatives or progeny thereof). For the avoidance of doubt, bone marrow samples and leukapheresis samples are deemed to be Human Biological Samples.

[***] Indication means [***].

[***] Indication means [***].

Indemnitee has the meaning given in Clause 15.3.

Intellectual Property Rights or **IPR** means any and all Patents, design rights, copyright, database rights, trade marks (whether or not any of them are registered or reasonably capable of being registered or patented including applications for registration of any of them), trade secrets, rights in Know-How, rights of confidence and all rights or forms of protection of a similar nature or having equivalent or similar effect to them subsisting anywhere in the world.

Joint Operating Committee has the meaning given in Clause 4.1(a).

Joint Ownership Parties has the meaning given in Clause 3.1(e).

Jointly Owned IPR means any Intellectual Property Rights that are discovered, invented, developed or otherwise conceived jointly by (a) employees or consultants of OTL or its Affiliates, on the one hand and (b) employees or consultants of MolMed or its Affiliates, on the other hand, in connection with the performance of the Services or the performance of any other obligations under this Agreement, but excluding any Arising OTL IPR.

Know-How means any proprietary or confidential technology, technical, scientific and medical information, methods of use, processes, techniques, ideas, inventions (excluding any inventions disclosed in any Patent or published Patent application), improvements, modifications, know-how, practices, trade secrets, chemistry, manufacturing and control data, quality control information, validation data and procedures, and pharmacological, toxicological and preclinical and clinical test data and results and regulatory information and marketing, promotion and other similar information and materials.

Licensed Field means any use or purpose whatsoever, including (i) use in the research, development, manufacture and commercialisation of cell and gene therapy products based on ex vivo transduction of stem cell for the treatment, palliation, diagnosis, cure or prevention of any human rare disease, disorder or condition and (ii) use in connection with the establishment and operation of the OTL Manufacturing Hubs.

Losses has the meaning given in Clause 15.1.

Manufacturing Fees means those fees calculated in accordance with **Schedule 1** and **Schedule 2**.

Manufacturing Licence means all licences, other than a Product License and OTL Licence IPR, necessary for or required by MolMed, according to the requirements of any Regulatory Authorities and/or Applicable Law, in connection with the Manufacture of any Product at the MolMed Facility.

Manufacturing Services means the services to be provided by MolMed pursuant to Clause 2.1(a) and 2.1(b).

Master Batch Record means the pro forma (blank) manufacturing batch record relating to the Products providing detailed instructions for execution of the Manufacturing process and for use in generating individual Batch Records.

Material Business Risk means, in relation to any Change of Control of MolMed, any risk that OTL, in its reasonable opinion determines could present a risk to OTL's competitive position, OTL's reputation, OTL's ability to protect or secure any Intellectual Property Rights of OTL or its Affiliates. Examples may include, but are not limited to, where the Person assuming Control of MolMed is a company with whom OTL is in dispute at that time, a company with whom OTL is or has been in litigation, a company that has competing programs or technologies, or a company that operates in jurisdictions or engages in business practices that are at odds with OTL's corporate ethical or anti-bribery and anti-corruption policies.

MolMed Enablement Know-How means any MolMed IPR that is either i) MolMed New IPR or ii) used by MolMed in the performance of the Services (but for the avoidance of doubt, excluding any Arising OTL IPR).

MolMed Enablement Licence has the meaning given in Clause 3.2(a).

MolMed Enablement Patent means any Patent which claims Know-How that is MolMed Enablement Know-How.

MolMed Facility means the manufacturing facility of MolMed at Via Olgettina 58, 20132 Milan, Italy and/or the manufacturing facility of MolMed at via Meucci 3 Bresso or such other European manufacturing facility of MolMed as shall have been approved in writing by OTL for the Manufacture of Products pursuant to this Agreement.

"**MolMed Fault**" means [***];

MolMed IPR means any Intellectual Property Rights, Know-How, information and materials that are Controlled by MolMed (whether at the Effective Date or at any time during the Term).

MolMed New IPR means any Intellectual Property Right that arises, is discovered, is invented or is developed by or on behalf of MolMed, independently of OTL Information and OTL Background IPR, through the performance of the Services or the performance of MolMed's other obligations under this Agreement, but excluding any Jointly Owned IPR.

New Indication Notice shall have the meaning given in Clause 2.3.

Non-Breaching Party has the meaning assigned to such term in Clause18.2(a).

Non-Commercial Product means Products for clinical or named use/compassionate use.

Non-Commercial Specification shall mean the specifications marked as "Safety" in the Product Specification File (PSF), (for clarity the Safety Specifications include sterility, microbiological control, and mycoplasma specifications).

MolMed Non-Enablement Know-How means any IPR which i) constitutes MolMed IPR and ii) is not MolMed Enablement Know How (whether at the Effective Date or during the Term), including but not limited to any IPR related to MolMed's proprietary products their manufacturing and analytical testing, MolMed's proprietary manufacturing processes and analytical methods deriving from internal research including IPRs identified in **Schedule 9** as well as any other IPR developed by MolMed out of the scope of the present Agreement through internal research activities or with Third Parties.

Non-Resource Charges means those charges relating to items other than resource to be calculated, invoiced and payable pursuant to **Schedule 3**.

OTL Background IPR means Intellectual Property Rights that are Controlled by OTL, including but not limited to any IPR related OTL's Product (including Manufacturing, as well as any other IPR provided or otherwise transferred by OTL to MolMed for the performance of the Services (whether at the Effective Date or at any time during the Term), but excluding any Arising OTL IPR.

OTL Competitor means any Person researching, developing or commercialising an ex vivo gene therapy for human use, either directly or via an Affiliate of that Person, in at least one of the [***] Indications and/or [***] Indications except where such activities are solely conducted on behalf of a Third Party that is not an Affiliate of that Person as a bona fide contract manufacturing business.

OTL Information means the information provided by OTL, or any Affiliate or Third Party engaged by OTL, to MolMed under this Agreement.

OTL Licences IPR means any Intellectual Property Rights that are necessary to ensure MolMed's freedom to operate in the use of the OTL Background IPR, OTL Information, OTL Materials for the performance of the Services under this Agreement.

OTL Manufacturing Hubs means any site or sites owned or contracted by OTL for the purposes of Manufacturing Products whether performed by Orchard directly or performed by a contractor on behalf of OTL.

OTL Materials means biological material [***] provided by OTL or residing at MolMed facilities but owned by OTL or to which OTL has been granted a right to use by Third Party. The OTL Materials as of the Effective Date are set out in **Schedule 5** and may be subject to change following the Effective Date prior written agreement between the Parties.

OTL Nominated User means any Third Party nominated by OTL (by written notice to MolMed) to benefit from the provision of Manufacturing Services under this Agreement.

Party or **Parties** has the meaning assigned to such term in the Preamble.

Patent means (a) all patents and patent applications in any country or supranational jurisdiction in the Territory, (b) any substitutions, divisions, continuations, continuations-in-part, provisional applications, reissues, renewals, registrations, confirmations, re-examinations, extensions, supplementary protection certificates and the like of any such patents or patent applications, and (c) foreign counterparts of any of the foregoing.

Payee has the meaning given in Clause12.5(d).

Payor has the meaning given in Clause12.5(d).

Person means any individual, partnership, joint venture, limited liability company, corporation, firm, trust, association, unincorporated organisation, governmental authority or agency, or any other entity not specifically listed herein.

Prior Agreement means a Strategic Manufacturing and Technology Development Agreement between GlaxoSmithKline Intellectual Property Development Limited and GlaxoSmithKline Trading Services Limited (together **"GSK-2"**) and MolMed dated 19 March 2015, which was amended and restated on 1 September, 2016.

Product means any Drug Product, or Viral Vector.

Product Licence means, with respect to any Product, each and every product licence (other than OTL Licences IPR), marketing authorisations or any other authorisation(s) (as the case may be) relating to the marketing, sales and/or distribution of that Product.

Quality Agreement means, with respect to any Product, the quality agreement signed by the Parties which shall set out the Parties' respective responsibilities for quality matters relating to the Manufacture of that Product.

Qualified Person means a person appointed by MolMed to undertake the responsibilities of a "Qualified Person" as defined in Article 51 of Directive 2001/83.

Receiving Party has the meaning given in Clause 13.1.

Regulatory Authority means any national or supranational governmental or regulatory authority which has responsibility in any country in the Territory over the Manufacture, development or commercialisation of Products, including, without limitation, the EMA, the European Commission, the AIFA and the FDA.

Relevant Know-How means any Know-How in the possession or Control of MolMed or any of its Affiliates (whether owned by MolMed, OTL, any of their respective Affiliates or any Third Party) which is necessary or reasonably useful in order to (a) Manufacture Products, (b) operate any OTL Manufacturing Hub or (c) create quality control processes and procedures relevant to the Manufacture of Products. For the avoidance of doubt, "Relevant Know-How" shall include all MolMed Enablement Know-How.

[***] Indications [***].

[***] Indication [***] means [***].

[***] Indication/s [***].

Resource Charges means those resource-based charges to be calculated, invoiced and payable pursuant to **Schedule 3**.

Sales Tax means any sales, purchase, value added or turnover tax as may be applicable in any relevant jurisdiction, including value added tax chargeable under or pursuant to the EC Council Directive (2006/112/EC).

Second Party has the meaning assigned to such term in Clause 18.2(b).

Service Fees means the Resource Charges and the Non-Resource Charges.

Services means the Manufacturing Services, the Development Services and the Technology Transfer Services.

Specifications means with respect to Commercial Product the Commercial Specification and with respect to Non-Commercial Product the Non-Commercial Specification.

Specific Equipment means any equipment owned by OTL that is (i) made available to MolMed by OTL; and/or (ii) purchased by MolMed and reimbursed by OTL. The Specific Equipment already at the disposal of MolMed are listed in **Schedule 6** hereto and shall be subject to the terms of this Agreement.

Statement of Work or **SOW** has the meaning given in **Schedule 3**.

Subcontract means each contract or agreement entered into by or on behalf of MolMed and any Person (whether or not in writing) under which that Person agrees to provide all or any part of the Services or perform any other obligation of MolMed arising under or in connection with this Agreement.

Subcontractor means a subcontractor of MolMed engaged by or on behalf of MolMed under a Subcontract. For the purpose of this Agreement entities qualified by OTL shall not be considered Subcontractors.

Technology Transfer Services means the technology transfer activities to be conducted by MolMed pursuant to Clause 2.1(d).

Term means the period commencing on the Effective Date and ending on the date when this Agreement is terminated in accordance with Clause 18.

Territory means the world.

Testing Laboratories means any Third Party instructed by MolMed to carry out tests on Products subject to OTL's consent pursuant to Clause 10.

Third Party means any Person other than i) OTL or MolMed or ii) an Affiliate of OTL or MolMed.

Third Party Claims has the meaning given in Clause 15.1.

Transduction Suite Reimbursement Amount shall mean the amount calculated in accordance with Clause 5.1 of **Schedule 4**.

Transduction Suite Termination Fee shall mean the amount calculated in accordance with Clause 5.3 of **Schedule 4**.

TT Nominee means any Affiliate of OTL or any strategic Third Party partner of OTL that OTL may nominate from time to time (by written notice to MolMed) to receive the benefit of the technology transfer of Relevant Know-How pursuant to **Schedule 3**.

U.S. means the United States of America and its territories and possessions.

Viral Vector means the key intermediate viral vector for each [***] Indication and/or [***] Indication, as applicable, as described in the relevant specification for that indication for use by OTL, its Affiliates and/or OTL's nominated contract manufacturers (including MolMed) in the Manufacture of the relevant Drug Product.

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY “[***]”, HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

1.2 Interpretation

(a) In this Agreement:

(i) subject to Clause 20.7 , any reference to a Party to this Agreement includes a reference to the successors or assigns (immediate or otherwise) of that Party;

(ii) any reference importing a gender includes the other genders; and

(iii) any reference to writing includes typing, printing and e-mail.

(b) In this Agreement each reference to a document is to that document as amended, varied, assigned or novated from time to time otherwise than in breach of this Agreement or that document.

(c) The headings in this Agreement do not affect its interpretation.

(d) The Schedules and annexes to this Agreement form part of it.

(e) If there is any conflict or inconsistency between:

(i) a term in the main body of this Agreement;

(ii) a term in any of the Schedules; and

(iii) any other document referred to or otherwise incorporated by reference into this Agreement,

the term falling into the category first appearing in the list above shall, unless it is expressly stated otherwise, take precedence. Nothwithstanding the above, if there is any conflict, discrepancy, or inconsistency between the terms of this Agreement and those of any Quality Agreement, the Quality Agreement shall control solely in respect of the allocation and scope of the parties’ quality-related performance obligations, and this Agreement shall control in all other respects, including in respect of financial obligations and risk allocation.

(f) Specific words indicating a type, class or category of thing do not restrict the meaning of general words following specific words, such as general words introduced by the word "other" or a similar expression. General words followed by specific words shall not be restricted in meaning to the type, class or category of thing indicated by the specific words. The words **including** and **include** shall mean "including without limitation" and "include without limitation" respectively.

(g) In this Agreement any reference to **costs and expenses** shall be construed as a reference to a party's internal costs and third party expenditure.

(h) Where any statement made by a Party in this Agreement is qualified by the expression **as far as it is aware** or any similar expression, that statement shall be deemed to be made on the basis of the best knowledge, as at the date that statement is made, of that Party’s management having made all reasonable enquiries.

(i) Clauses 1.2(a) to (h) apply unless the contrary intention appears.

2. SERVICES AND COLLABORATION

2.1 Overview

This Agreement sets forth the structure, rights, restrictions and obligations under which MolMed agrees to perform the Services. In particular, pursuant to and subject to the terms and conditions set forth in this Agreement, MolMed will:

(a) provide Manufacturing Services for Viral Vector to OTL in accordance with the terms set out in **Schedule 1**;

(b) provide Manufacturing Services for Drug Product to OTL in accordance with the terms set out in **Schedule 2**;

(c) provide Development Services to OTL in accordance with the terms set out in **Schedule 3**;

(d) conduct Technology Transfer Services in accordance with the terms set out in **Schedule 3**;

(e) reserve [***] Exclusive Transduction Suites for the exclusive benefit of OTL for use in connection with the Manufacturing Services in accordance with the terms set out in **Schedule 4** and commit a total of [***] for the exclusive benefit of OTL for use in connection with the Manufacturing Services for Drug Product in accordance with the terms set out in **Schedule 4.**

With effect from the Effective Date this Agreement supersedes the Prior Agreement.

Pursuant to and subject to the terms and conditions set forth in this Agreement, each Party shall co-operate with, and provide reasonable support and assistance to, the other Party in connection with the provision and receipt of the Services and in performing its obligations under this Agreement.

2.2 Exclusivity

(a) During the Term, subject to OTL complying with its obligations under section 2.2 lett. b) and 2.4 lett a) below, MolMed shall not (whether on its own, or with or through any Affiliate or Third Party):

(i) provide any services to a Third Party in connection with the development or manufacture in the [***] Field of any product that is targeted at [***]; or

(ii) grant any licences in the [***] Field under any MolMed IPR permitting any Third Party to use such MolMed IPR for the purposes of developing or manufacturing any product that is targeted at any [***]; provided however, that in the event OTL provides written consent to MolMed, MolMed may grant a license under the MolMed IPR to [***] for the purpose of conducting activities on an [***]; or

For the avoidance of doubt, the provision of Manufacturing Services by MolMed to any OTL Nominated User in accordance with this Agreement shall not constitute a breach of this Clause 2.2(a).

(b) It is clearly understood that the exclusivity rights granted under this clause 2.2 in each [***]. In the event that exclusivity rights terminate under this clause 2.2 (b), [***].

2.3 New Indications

(a) The Parties acknowledge and agree that, as at the Effective Date, the Services shall only be provided with respect to the [***]. If, at any time during the Term, OTL requires MolMed to perform Services in relation to any indication that is [***], OTL shall notify MolMed in writing (a New Indication Notice). Where OTL requires the performance of the Service on exclusive basis, MolMed will have the right to withhold its approval to provide such Service with respect to that indication if in its reasonable opinion determines that the provision of exclusive services for OTL i) infringes or may infringe any Intellectual Property rights of a Third Party IP or ii) that it is not profitable or feasible for MolMed or iii) potentially infringe good faith and fair dealing duty, including if MolMed entered into business discussion with a Third Party with respect to the relevant indication.

(b) Where the Parties agree the commencement of the Services for an [***] included in a New Indication Notice, such new indication shall be deemed to be an [***] Indication for the purposes of this Agreement. It is clearly understood that Clause 2.2 b) shall apply with respect to such [***].

(c) Where the Parties agree the commencement of the Services [***] with respect to any indication included in a New Indication Notice, such indication shall be considered an [***] and therefore MolMed will [***].

(d) Where the Joint Operating Committee approves the commencement of the Manufacturing Services with respect to any indication included in a New Indication Notice, with effect from the date of such approval (or such other date as the Joint Operating Committee determines) within [***] days from the completion of the Development Service and in any case prior the commencement of any Manufacturing Service, the Parties shall agree, with respect to that [***]:

(i) the Quality Agreement relevant to that [***];

(ii) the Specifications for that [***];

(iii) any Technology Transfer Services to be provided with respect to that [***];

(iv) the Manufacturing Fees per Batch that will apply to the Manufacture of Product for that [***];

(v) the lead times that will apply with respect to the Manufacture of Product for that [***];

(vi) any other matters which need to be agreed between the Parties in order to commence the Manufacture of Product for that [***]; and

(vii) [***].

In agreeing the matters listed in paragraphs (i) to (vii) above, each Party shall act reasonably and in good faith, with the intent of commencing provision of Manufacturing Services with respect to [***] as reasonably practicable after the Joint Operating Committee approval has been obtained.

2.4 **[***] Indication List**

a) Subject to [***].

2.5 Replacement of a [***]

(a) OTL will be entitled to propose revision to the [***].

(b) OTL shall [***].

(c) Within [***].

3. GRANT OF LICENCES

3.1 Ownership of Intellectual Property Rights

(a) All Intellectual Property Rights belonging to a Party prior to the Effective Date shall remain vested in that Party. Except as otherwise expressly agreed, each Party shall continue to own existing Intellectual Property Rights without conferring any interests therein on the other Party. For the avoidance of doubt, ownership of any Intellectual Property Rights that arose, were discovered, were invented or were developed through the performance of the obligations under any Prior Agreement shall be determined in accordance with the terms of that Prior Agreement.

(b) OTL, or its nominee, shall be the sole and absolute owner of all Arising OTL IPR and OTL (or its nominee) shall have the exclusive right, at its discretion, to file patent applications, or seek other intellectual property protections, for any Arising OTL IPR anywhere in the world.

(c) MolMed shall, at OTL's expense, execute all such documents, perform all such acts and provide all such assistance as OTL may reasonably request to vest the Arising OTL IPR in OTL or its nominee (as the case may be) together with all rights which may belong or accrue thereto and/or to enable OTL or its designee to file, prosecute, maintain or renew any applications for registration of any of the Arising OTL IPR.

(d) MolMed, or its nominee, shall be the sole and absolute owner of all MolMed New IPR and MolMed (or its nominee) shall have the exclusive right, at its discretion, to file patent applications, or seek other intellectual property protections, for any MolMed New IPR anywhere in the world.

(e) OTL and MolMed (the **Joint Ownership Parties**) shall each own an undivided one-half interest in and to all Jointly Owned IPR with full ownership rights in and to any field and each Joint Ownership Party shall have the right, subject to the rights and licences granted under, and the other provisions of, this Agreement, to freely exploit, transfer, license or encumber its rights in any such Jointly Owned IPR without the consent of, or payment or accounting to, the other Joint Ownership Party, and each Joint Ownership Party waives any right it may have under any Applicable Law to require such payment, accounting or consent. This Clause 3.1(e) shall survive termination of this Agreement howsoever caused. Upon becoming aware of any Jointly Owned IPR, a Party shall notify the other Party and, upon receipt of any such notification, the Parties shall meet to discuss and agree appropriate arrangements with respect to the filing, prosecution, maintenance and enforcement of the relevant Jointly Owned IPR.

3.2 Licence of MolMed's Rights

(a) Subject to Clause 18.3 below, MolMed hereby grants to OTL [***] to the MolMed Enablement Know-How and each MolMed Enablement Patent in the Licensed Field in the Territory (the "**MolMed Enablement Licence**).

(b) Subject to Clause 18 , the MolMed Enablement Licence shall be:

(i) [***] with respect to the [***] Field; and

(ii) [***] Licensed Field.

3.3 **Licence of OTL's Rights**

(a) OTL hereby grants to MolMed an irrevocable, royalty free, fully paid up, non-exclusive licence, with the right to grant sublicences (through multiple tiers, but subject always to Clause 20.7 to use the Arising OTL IPR, the OTL Background IPR and the OTL Licence IPR strictly for the performance of the Services and the performance of MolMed's other obligations under this Agreement.

(b) OTL hereby grants to MolMed a perpetual, irrevocable, royalty free, fully paid up, non-exclusive licence, with the right to grant sublicences (through multiple tiers), to use the Arising General OTL IPR in the performance of development activities and cGMP activities for the manufacturing of viral vectors and/or cell products for projects for itself and for Third Parties in indications other than the [***].

3.4 **MolMed Non – Enablement Know-How**

(a) MolMed shall promptly notify OTL JOC members in writing (by email) of each MolMed Non-Enablement Know-How which it (acting reasonably) considers could be useful to the performance of the Services (a **Non-Enablement Know-How Notice**).

(b) Following receipt of any Non-Enablement Know-How Notice, OTL or its designee may elect (by notice in writing to MolMed) to i) appoint MolMed to perform a feasibility study to evaluate the Non-Enablement Know-How, which will be paid by OTL as a Service Fee. Within [***] days after the completion of the feasibility activities, OTL shall have the right to provide written notice to MolMed of its will to negotiate a licence to use the relevant MolMed Non-Enablement Know-How in the Licensed Field (or any part of the Licensed Field) . If OTL does elect to negotiate a licence to the relevant MolMed Non-Enablement Know-How, the Parties shall enter into negotiations in relation to the same (acting reasonably and in good faith) with a view to agreeing the terms (including any financial terms, as well as exploitation rights on the intellectual property rights eventually arising) upon which such licence will be granted. The terms of the agreement will fairly reflect the inventive contribution of the Parties to such arising intellectual property rights. It is understood that MolMed shall retain sole ownership in the Non-Enablement Know-How. OTL acknowledges and agrees that no other right or license to Non-Enablement Know-How is granted or implied other than as explicitly provided in this Agreement. Nothing shall restrict MolMed's right to disclose, use, sell, assign, distribute or otherwise transfer the Non-Enablement Know-How to any Third Party for any purpose.

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

(c) For the sake of clarity, the feasibility activities performed or being performed by MolMed with respect to [***] shall be deemed to be a feasibility study pursuant to clause 3.4 (b) above.

(d) MolMed shall not use any MolMed Non-Enablement Know-How in the provision of the Services until such time as the Parties have agreed the licence for OTL's use of that MolMed Non-Enablement Know-How in accordance with Clause 3.4(b).

(e) For the sake of clarity the MolMed Non-Enablement Know-How Notices provided up to and no later than June 30, 2020 and in accordance with section 3.4(a) of the Prior Agreement are as follows: [***].

3.5 **Third Party Infringement**

(a) If MolMed becomes aware at any time that any infringement or unauthorised use of any of the Arising OTL IPR or OTL Background IPR is occurring, threatened or likely, MolMed shall promptly provide to OTL all such information as it has in relation thereto and shall promptly provide all such assistance which OTL reasonably requests in taking any action or proceedings in relation thereto. For the avoidance of doubt, OTL shall have the exclusive right but not the obligation to take any action or proceedings against any Third Party in relation to any Arising OTL IPR and any OTL Background IPR.

(b) [***]. MolMed shall use Commercially Reasonable Endeavours to provide the Services without knowingly using any Third Party's Intellectual Property Rights. MolMed shall promptly inform OTL if it becomes aware that the Services or part thereof may potentially interfere with any Third Party's Intellectual Property Rights to permit the Parties to perform all analysis required to evaluate a potential infringement and discuss the actions required to avoid any infringement. It is intended that the responsibility to take any action required to avoid or anticipate any infringement will be assumed by i) OTL for any potential infringement deriving from the use by MolMed of any OTL Material, OTL Information or OTL Background IPR or OTL Arising IPR in the performance of the Service, or ii) by MolMed for any potential infringement deriving from the use by MolMed of any MolMed Enablement Know How or MolMed New IPR in the performance of the Services.

(c) Any modification to any technical and/or scientific aspect of the Services will be discussed between the Parties which shall use Commercially Reasonable Endeavours to investigate the relevant Patent coverage of Third Parties relating to any such modification and promptly inform the other of the results of such investigation. If either Party identifies any relevant Third Party Patent(s) MolMed shall not proceed to incorporate the modification into the Services without OTL's prior written consent.

4. GOVERNANCE

4.1 Establishment of the Joint Steering Committee

(a) The Parties shall, within a reasonable period of time after the Effective Date, establish a joint operating committee (the **Joint Operating Committee**), which shall remain in place for the Term.

(b) The Joint Operating Committee shall consist of an equal number of representatives from both OTL and MolMed (up to a maximum of three (3) representatives per Party). Each Party shall select its Joint Operating Committee representatives with a view to covering the key elements of the Services to be provided under this Agreement and shall ensure that its selected representatives are of suitable authority and seniority. Each Party may replace any or all of its representatives on the Joint Operating Committee with a new representative of equal experience and seniority at any time. Each Party may invite from time to time (at its discretion and with the consent of the other Party, such consent not to be unreasonably withheld or delayed) additional employees or consultants to attend Joint Operating Committee meetings to address specific issues discussed at the Joint Operating Committee meetings, provided that such additional employees and consultants are in a reasonable number so as not to disturb the work and administration of the Joint Operation Committee meetings.

4.2 Joint Operating Committee Responsibilities

The Joint Operating Committee is responsible (i) for strategic oversight and management of the Services; (ii) to settle disputes or disagreements not resolved by the Sub-committees (as defined below) unless otherwise indicated in this Agreement; (iii) to discuss major issues regarding the performance of Services; and (iv) to carry out such other activities as are expressly allocated to the Joint Operating Committee hereunder.

4.3 Meetings

The Joint Operating Committee shall meet at least once every three (3) months and more frequently if agreed between the Parties. Such meetings shall be held at such times as are mutually agreed upon by the Joint Operating Committee. Meetings may take place in person or by video conference or telephone conference or such other means as the Joint Operating Committee shall decide, *provided*, *however*, that all members of the Joint Operating Committee shall meet in person at least once in each Contract Year, unless otherwise agreed by the Parties. Meetings held in person shall alternate between OTL and MolMed designated locations, sequentially. The first meeting shall be held at OTL's facilities.

4.4 **Administrative Matters**

The Joint Operating Committee shall establish its own procedural rules for its operation consistent with the terms of this Clause 4.4. A chairperson for the Joint Operating Committee shall be appointed from among its members. The chairperson for each meeting of the Joint Operating Committee shall alternate between an OTL representative and a MolMed representative, OTL being responsible for designating the chairperson for the first meeting. The chairperson for a meeting shall be responsible for providing an agenda for each meeting, taking into consideration the other Party proposal, at least [***] Business Days in advance of such meeting and leading the meeting for which he/she is chairperson and for calling the next meeting of the Joint Operating Committee. One member representing the Party that appointed the chairperson for the meeting shall serve as secretary of that meeting. The secretary of the meeting shall prepare and distribute (within [***] days following each meeting) to all members of the Joint Operating Committee the draft minutes of the meeting. Such draft minutes shall provide a description in reasonable detail of the discussions held at the meeting and a list of any actions, decisions or determinations approved by the Joint Operating Committee at such meeting. The minutes of each Joint Operating Committee meeting shall be approved or disapproved by each Party's Joint Operating Committee representatives, and revised as necessary, as soon as reasonably practicable and in any event no later than the next meeting of the Joint Operating Committee. Final minutes of each meeting shall be distributed promptly thereafter to the members of the Joint Operating Committee by the relevant chairperson.

4.5 Decision Making

All decisions of the Joint Operating Committee shall be made by the unanimous decision, with the representatives of each Party who are members of the Joint Operating Committee collectively having one vote in any matter requiring the approval of the Joint Operating Committee. If the Joint Operating

Committee is unable to resolve a Dispute regarding any issue, the matter shall be resolved pursuant to the dispute resolution process set forth in Clause 19.

4.6 Appointment of sub-committees

The Joint Operating Committee is empowered to create technical sub-committees of itself as it may deem appropriate or necessary. Each sub-committees shall meet at least twice per month and more frequently if needed. Such meetings shall be held at such times as are mutually agreed upon by the Parties. Meetings may take place by video conference or telephone conference. Each such sub-team or subcommittee shall report to the Joint Operating Committee, who shall have authority to approve or reject recommendations or actions proposed subject to the terms of this Agreement. No sub-team or subcommittee shall have authority to make any decision binding upon the Joint Operating Committee or the Parties. The Parties acknowledge and agree that, at the first meeting of the Joint Operating Committee, the Joint Operating Committee shall establish a joint development committee (JDC) which shall have responsibility for monitoring the performance of the Development Services.

4.7 Limitations on the Authority of the Joint Operating Committee

Decision-making by the Joint Operating Committee shall be by consensus of representatives present at the meeting provided however that, unless vesting of rights is expressly provided for in this Agreement or the Parties expressly so agree in writing, any amendments to this Agreement may only be made in accordance with Clause 20.2.

Where any matter requiring a decision of the Joint Operating Committee is an emergency or requires an urgent decision prior to the next scheduled meeting of the Joint Operating Committee, the Parties shall, as soon as reasonably practicable, convene an ad hoc meeting of the Joint Operating Committee at which the relevant decision can be made on a "fast-track" basis and of which the minutes shall be circulated as soon as reasonably possible thereafter. The chairperson and secretary shall be from the Party convening the ad hoc meeting of the Joint Operating Committee.

4.8 **Books and Financial Records**

Any financial books and records to be maintained under this Agreement by a Party shall be maintained in accordance with International Financial Reporting Standards (IFRS), consistently applied, except that the same need not be audited.

MolMed shall keep complete systematic records related to the Services performed under this Agreement. Such records shall include any material operational documentation pertaining to the Services, including records relevant to any costs or expenses incurred by MolMed on behalf of OTL, any financial records, procedures and such other documentation pertaining to the Services.

Upon the written request of OTL with at least [***] days prior written notice and not more than once in each Contract Year, MolMed shall permit no more than two auditors of an independent accounting firm selected by OTL and reasonably acceptable to MolMed to have access during normal business hours to the records. The accounting firm shall disclose to OTL only whether or not the record is correct and the amounts and reasons for any discrepancies. In accessing MolMed's premises and/or the further premises relevant to this Agreement to perform audits, the accounting firm shall not stop or materially impair the ordinary working activities, and minimize as reasonably possible the inconvenience relating to the audit and the permanence at MolMed premises.

OTLshall bear any costs [***] incurred for the purposes of exercising its audits and/or inspections rights. Should, however, any audit or inspection reveal a non-insignificant discrepancy, and in any case higher than [***] of the amount paid by OTL in the relevant Contract Year, MolMed shall bear demonstrated and reasonable audit costs and refund them to OTL within [***] days from written request by the latter.

MolMed shall preserve all such records for the greater of seven (7) years. In the event a legal matter arises requiring preservation of certain records, MolMed shall suspend destruction of such records as requested by OTL.

4.9 **MolMed Reporting Obligations**

No more than once in each Contract Year, OTL shall have the right to request a meeting with the MolMed's CEO and/or CFO and/or any other relevant senior management representative of MolMed for the purposes of discussing and understanding MolMed's corporate strategy and financing plans. Following receipt of any such meeting request, MolMed shall promptly (and in any event no later than [***] days after the request) organise the meeting at a time that is mutually convenient to both Parties. For the avoidance of doubt, nothing in this Clause 4.9 shall require MolMed to disclose any information to the extent doing so would put MolMed (or its CEO, CFO or other representative) in breach of any Applicable Law, including Market Abuse Provisions, as defined in clause 13.3.

4.10 Project Management

Each Party shall appoint a project manager to act as the primary contact for such Party in connection with matters related to the performance of the Service (each a "**Project Manager**"). The Project Manager is responsible for management of the ongoing activities related to the Services. A Party may replace its Project Manager(s) at any time and from time to time for any reason by providing advance written notice of the change to the other Party.

4.11 MolMed Change of Control

Without prejudice to any other rights or remedies of OTL, if there is a Change of Control [***] of MolMed:

(a) OTL shall have the right to and MolMed shall make its best effort to procure that OTL can meet appropriate representatives from the entity taking Control of MolMed and/or MolMed's new management on a regular basis and not less than once every [***] days during [***] period after the date of the Change of Control in order to discuss MolMed's compliance with its obligations under this Agreement and any organisational changes to MolMed that will, or would be reasonably likely to, impact OTL; and

(b) if the entity taking Control of MolMed is an OTL Competitor, the Parties shall establish effective procedures, systems and security measures to ensure that there is no transfer of Know-How or Intellectual Property Rights owned or controlled by OTL to the applicable OTL Competitor or use of the same in the provision of any services to, or on behalf of, the applicable OTL Competitor (save as is permitted in accordance with the licence granted at Clause 3.3(b)). OTL agrees that AGC Inc. and any of its subsidiaries and/or affiliates shall not be deemed to be OTL Competitors.

For the avoidance of doubt, subject to 4.12(b), in a Change of Control situation, this Agreement will automatically transfer to the entity taking Control of MolMed in its entirety, MolMed shall provide all reasonable cooperation to OTL, facilitating the exchange of information that may be necessary or useful to continuewith any negotiations or discussions between OTL and the entity taking Control of MolMed at the time of the Change of Control.

4.12 Notification of Safety Hazards

Either party will inform and keep the other informed of all safety hazards and changes in regulations and guidance (statutory or otherwise) which such Party knows or believes to impact the use, handling, storage, labelling, transport, treatment and disposal of Products and MolMed will ensure that relevant consignments are safe, packaged, labelled so as to prevent any health risk to Persons, property or the environment and properly marked with the appropriate internationally recognised danger symbols and that prominent hazard warnings appear in English (and/or any other language specified by OTL) on all packages and documents.

5. SUPPLY OF OTL MATERIALS

5.1 In order to enable MolMed to properly discharge its obligations, OTL shall timely provide MolMed with

(i) any OTL Materials necessary for the performance of the Services;

(ii) relevant documentation set forth in the Quality Agreement;

(iii) all necessary information in its possession about any actual or potential health and/or environmental Hazards associated with exposure to the handling, storage, use, or disposal of the OTL Materials;

(iv) any further documentation requested by MolMed necessary to perform its obligations under the Agreement and;

(v) any updated information about such health or environmental Hazards that come to its attention.

5.2 MolMed agrees that the OTL Materials will: (i) be used solely for, and in compliance with, the Services and provision of Services, (ii) be used in compliance with all Applicable Laws; (iii) not be transferred to a Third Party (except for i) Approved Subcontractor and ii) Subcontractor(s) approved by OTL pursuant to clause 20.7 c)) without the prior written consent of OTL; (iv) be identified in such a way as to be able at all times to clearly distinguish OTL Materials from products and materials belonging to MolMed, or held by it for a third party's account and labelled as OTL property at all times.

5.3 The delivery of the OTL Materials shall be made on the basis [***] to MolMed Facility. OTL shall be solely responsible for the importation of the goods, MolMed will cooperate with the designated carrier, at OTL's request and expense, to provide the designated carrier with any information necessary to perfom custom activity for OTL.

5.4 In the event that a delay in supplying OTL Materials impacts on MolMed ability to meet the Manufacturing Forecast in accordance with **Schedule 1** and **Schedule 2**, the cancellation fees set forth **Schedule 1** and **Schedule 2** shall apply. MolMed shall comply with any storage specifications and/or conditions specific to the OTL Materials as defined in the Quality Agreement. Where applicable, MolMed shall be responsible for the transport of any OTL Materials from its storage site up to the Facility. The ownership of OTL Materials shall remain at all times with OTL during the term of the storage by MolMed and only the transfer of the risk to MolMed shall occur upon delivery of the OTL Materials at MolMed's designated site.

5.5 Subject to the terms of the Quality Agreement, MolMed shall store the OTL Materials [***] for the entire duration of the material shelf life. MolMed will periodically inform OTL about expired

OTL Material. If OTL does not require, as notified in writing MolMed to store the expired OTL Material within [***] Business Days, then MolMed will be entitled to destroy the expired OTL Material at OTL cost.; or OTL shall collect OTL Material at MolMed Facilities on Ex Works basis within [***] days from MolMed notice. In the event the quantity of OTL Material may considerably impact MolMed storage capacity, MolMed shall have the right to request a meeting with OTL, wherein the Parties shall discuss and use their best effort to agree on the feasibility of the storage and any fees associated with it, Schedule 8 shall be amended accordingly.

5.6 The list of OTL Materials & Critical Materials in Schedule 5 may be amended from time to time upon written agreement between the Parties. Such agreement may be reached by email or as a side letter to this Agreement.

6. SPECIFIC EQUIPMENT

6.1 The Parties will agree on the Specific Equipment that will be required to perform the Services. Prior to the purchase of Specific Equipment, MolMed will inform OTL about the availability of equipment located at the Facility which i) MolMed is entitled to use for the performing of the Services, and ii) may be suitable for the intended use. It is clearly understood that i) OTL shall be responsible for ensuring that the relevant Specific Equipment or the equipment made available by MolMed is suitable for its intended use. Where a new equipment is required for the performance of the Service, MolMed shall notify OTL if a suitable equipment is available at MolMed Facility. If OTL wishes MolMed to use such equipment for the performance of the Service, OTL shall notify MolMed in writing and the Parties will agree upon a reasonable fee if applicable based on mutual agreement by the Parties to be paid by OTL under the relevant Statement of Work.

6.2 OTL shall deliver the Specific Equipment [***]. Risk of loss and damages to the Specific Equipment shall be borne by [***]. MolMed shall be responsible for [***].

6.3 During the duration of the Agreement MolMed shall [***].

6.4 Prior written notice to OTL, MolMed will be [***].

6.5 If required by OTL, the Specific Equipment will be purchased by MolMed [***].

6.6 In the event the type or the quantity of the Specific Equipment, which are not located in an Exclusive Transduction Suite, may require plant adaptations, limit substantially the space, and/or create safety hazards, MolMed shall have the right to request a meeting with OTL, wherein the Parties shall discuss the feasibility of Specific Equipment installation, potential risk and cost to be borne by OTL with regards to the same.

6.7 All quality related activities involving Specific Equipment will be [***].

6.8 Upon termination or expiry of the Agreement, [***].

6.9 OTL shall appropriately dismantle and remove [***] Specific Equipment within [***]. During this period MolMed shall co-operate and permit reasonable access to its premises to allow OTL, or OTL sub-contractors, to dismantle and remove Specific Equipment.

6.10 MolMed will be responsible for any equipment, other than Specific Equipment, located at the Facility.

6.11 The list of Specific Equipment in Schedule 6 may be amended from time to time upon written agreement between the Parties. Such agreement may be reached by email or as a side letter to this Agreement.

7. DELIVERABLE AND DOCUMENTATION

7.1 MolMed shall i) retain complete, accurate and authentic documents and records created by MolMed for each Product, as required by GMP ii) provide OTL with or access to the documents mentioned in **Schedule 7.**

7.2 The list of documents may be amended from time to time upon written agreement between the Parties. Such agreement may be reached by email or as a side letter to this Agreement.

7.3 During an audit, OTL will have access to any other documentation which is reasonably necessary to exercise OTL auditing rights in accordance with Clause 11. [***].

7.4 Documents and records created by MolMed shall be in Italian or English. The specific documents to be drafted in English or for which MolMed will provide English language translations are outlined in **Schedule 7.** Any further language translations shall be managed by OTL. However all deviations, non-conformances and hand written notes on batch records as part of MolMed's batch dispositions will also be provided by MolMed with English translations. [***].

7.5 Delivery of Deliverables to OTL will be made by [***]. The Deliverables shall be collected by OTL's designated carrier at MolMed Facility during normal business hours (Monday to Friday, excluding statutory holidays in Milan and London).

8. QUALIFIED PERSONS

MolMed shall at all times employ a Qualified Person as defined by Article 48 of Directive 2001/83/EC who shall be responsible, in accordance with Applicable Law, for confirming by his/her signature on the-appropriate Batch Certificate that each Batch of Product conforms with the requirements of the Product Specification File and is Manufactured in accordance with cGMP and Marketing Authorisation/Clinical Trial Authorisation. OTL will provide MolMed with: (i) copy (or the relevant part) of the regulatory documentation approved by the reference regulatory authorities concerning the manufacture of Product, and (ii) the Services or the CMC section as necessary to allow MolMed's Qualified Person to certify the Product in accordance with the Applicable Law (included but not limited to Legal Decree 219/2006).

9. **REGULATORY COMPLIANCE**

9.1 OTL shall have overall responsibility regarding all contacts with the relevant Regulatory Authorities and shall be solely responsible for filing all regulatory documents required by such Regulatory Authorities specific to the Product.

9.2 Prior to the submission of any communication or regulatory filing concerning the manufacture of Product, the Services or the chemistry, manufacturing and controls ("CMC") section containing, i*nter alia*, information and manufacturing data generated under this Agreement, OTL agree to inform MolMed in advance in a timely manner. MolMed shall review and approve these communications and any regulatory filings concerning the manufacture of Product and the Services prior to their submission, such approval shall not be unreasonably withheld.

9.3 Prior the submission, MolMed shall review and approve any changes made by OTL to those parts of the CMC section of the regulatory documentation to the extent they contain information about manufacture of Product, OTL shall provide such review and approval in a timely manner, such approval shall not be unreasonably withheld. In the event that such changes are supported by data generated by OTL, OTL shall provide MolMed with the relevant supporting documentation.

9.4 OTL shall timely inform MolMed in writing in order to arrange any inspection, associated with any commercial licence application OTL, of the MolMed Facility by any Regulatory Authority. As soon as reasonably practicable the Joint Operating Committee shall meet to discuss the activities plan [***] to arrange such inspection.

9.5 To the extent such response may impact MolMed's ability to Manufacture Product under this Agreement or OTL's Product Licences, MolMed shall give prompt written notice to, and consult with, OTL upon receipt of any such communication or request for information from a Regulatory Authority, and OTL shall be entitled to review any proposed response or submission from MolMed before it is given to a Regulatory Authority.

9.6 MolMed shall allow and shall be responsible for handling inspections of the MolMed Facility and any other relevant sites and premises as may be requested by such Regulatory Authority, the findings of which, to the extent they affect the Manufacture of Product, shall promptly be made known in writing to OTL. MolMed shall, to the extent practicable, notify OTL in advance of any such inspection relating to the Manufacture of Product and provide OTL with the opportunity to attend, subject to any reasonably imposed confidentiality obligations.

9.7 OTL shall be responsible for preparing and submitting any regulatory submission dossiers in respect of any Product and MolMed shall be responsible for drafting and providing materials for such dossiers on behalf of OTL in a form acceptable to OTL subject [***], pursuant to clause 9.10. In each case, such responsibilities will be carried out in accordance with cGMP and EUTCD or as may be required by a Regulatory Authority and each Party shall be responsible for maintaining the same as required by any Regulatory Authority and for updating the same where necessary to implement any improvements or changes agreed by the Parties in writing and resulting from any work conducted by the Parties or changes made under this Agreement.

9.8 OTL shall be entitled on a confidential basis to disclose information contained in any relevant regulatory dossiers to its Affiliates, sub-licensees and distributors subject to OTL obligation pursuant to Clause 13. OTL may at any time disclose any such information to any Regulatory Authority or any other regulatory or governmental authority provided that it exercises all Commercially Reasonable Endeavours to have confidential treatment afforded to such information.

9.9 MolMed shall Use Commercially Reasonable Endeavours to respond promptly and in a timely manner to any questions of a regulatory nature relating to any Product or its Manufacture raised either by OTL, its Affiliates, sub-licensees or distributors, any OTL Nominated User or by a Regulatory Authority.

9.10 Any regulatory services provided by MolMed related to either obtaining or maintaining regulatory approval for the Product in the Territory, including the handling of Regulatory Authority inspections of [***].

10. MANUFACTURING CHANGES

10.1 **Changes by MolMed**. MolMed shall not change the MolMed Facility at which Product is Manufactured (or the site of Manufacture of any registered Materials used in any Product), or the registered Materials, or process or plant used in the Manufacture of any Product, or the Testing Laboratories or the analytical testing methods without first obtaining written consent from OTL to such change, such consent not to be unreasonably withheld or delayed (but acknowledging that such change may require OTL and/or MolMed to obtain approval from relevant Regulatory Authorities).

10.2 The changes encompassed by Clause 10.1 above shall be limited to such changes which may reasonably be expected to have a potential impact on the quality or physical characteristics of the Product, or OTL's regulatory obligations with respect to the Product or the likely success of delivery of the Product to the patient. Any change to be agreed pursuant to Clause 10.1 shall be notified and managed in accordance with the relevant Quality Agreement.

10.3 Notwithstanding Clause 10.1 above, in no case shall MolMed effect any relevant change without first ensuring that the change will result in a comparable product and obtaining written approval from OTL. Where applicable, OTL, as the regulatory sponsor of the Product, will be solely responsible for engaging with, and seeking approval for such change from, the relevant Regulatory Authority. MolMed agrees to use Commercially ReasonableeEndeavours, as requested from time to time by OTL, to assist OTL with respect to such interactions with, and requests from, any Regulatory Authority. The comparability of Product Manufactured following the proposed change with Product Manufactured prior to the proposed change will be assessed by the Parties before submission to each relevant Regulatory Authority. MolMed shall reasonably cooperate with OTL and will provide OTL with all information and data (including Data) OTL may require in order to satisfy OTL that the proposed change will result in a comparable product. Upon full written endorsement by each relevant Regulatory Authority and approval of OTL, MolMed will implement such approved change. OTL will provide MolMed with such information as necessary regarding the regulatory approval as reasonably necessary to effect the changes, maintain compliant documentation and allow the Qualified Person(s) to discharge their role.

10.4 Subject to Clause 10.1 and 10.2 above, [***].

10.5 **Change by OTL**. Except as otherwise expressly set forth to the contrary in the Quality Agreement, if OTL desires to change registered materials, reagent or process or equipment used in the Manufacture of any Product, or the Testing Laboratories or the analytical testing methods, then Parties shall hold a meeting to discuss such changes as appropriate including [***].

10.6 **Change by Regulatory Authority.**

10.7 If a Regulatory Authority requests or requires that a change be made to the Manufacturing Process or if changes to the Manufacturing Process are required in order to comply with Applicable Law (including, without limitation, cGMP), then the Parties shall meet to discuss the action plan [***] with a target completion date. OTL shall [***].

10.8 **Change to Specification and Manufacturing Process.** The Specifications and the Master Batch Record may only be changed by agreement in writing by the Parties. For the avoidance of doubt, OTL, as the regulatory sponsor of each Product, will be solely responsible for seeking such approval for such specification changes from the relevant Regulatory Authority and responding to any request for a change to any Specifications received from any relevant Regulatory Authority. MolMed agrees to use its reasonable endeavours, as requested from time to time by OTL, to assist OTL with respect to such interactions with, and requests from, any Regulatory Authority. OTL will provide MolMed with such information regarding the regulatory approval as reasonably necessary to effect the changes, maintain compliant documentation and allow the Qualified Person(s) to discharge their role. Neither Party shall unreasonably withhold its agreement to any change in the Specifications or the Master Batch Record requested by the other Party. [***].

11. AUDITING AND INSPECTION

11.1 During the term of this Agreement, [***], OTL shall have the right to enter and inspect free of charge the MolMed Facility for the purpose of making quality assurance audits and assessments of the Manufacturing Facilities and of the procedures and processes used by MolMed in the manufacture of the Product in accordance with the Quality Agreement, provided that [***], in accordance with the terms and conditions of this Agreement, and the Quality Agreement (if applicable).

11.2 In addition, MolMed shall allow OTL to access – at the terms and conditions set forth under the Quality Agreement – to MolMed Facility in the event that: i) major deviation might arise; or ii) OTL has reasonable grounds to suspect that MolMed is in material breach of any obligations under this Agreement; in such event, OTL shall be allowed to conduct a for cause or directed audit solely in respect to the suspected breach. It remains understood that (i) no more than two auditors are permitted to be present during such audit; (ii) the audit is conducted during normal business hours at a time on which the Parties have mutually agreed and upon prior reasonable written notice; and OTL is bound to provide evidence of the suspect in writing, providing to MoLMed the relevant proofs under its possession for the purposes hereof by written notice [***] days in advance up to the date of inspection. In th event such audit does not reveal a major deviation or a material breach of MolMed obligations, [***].

11.3 If required for OTL's submission of any regulatory filing to a relevant Regulatory Authority MolMed shall permit representatives of the relevant Regulatory Authority, or cause an auditor of an appropriately qualified third party mutually agreed on by MolMed and OTL, to conduct a GMP compliance audit at the Facility (mock inspections), [***]. As a condition to allowing such third party-auditor to conduct a GMP compliance audit at the Facility, MolMed will require such third party-auditor to execute a non-disclosure agreement with MolMed. The third party-auditor shall not have the right to copy any notes, data, records or other documentation maintained by MolMed. The contents of such third party-auditor's audit report shall be limited to the minimum information legally required for OTL's submission of the applicable Regulatory Filing or necessary for approval thereof by the relevant Authority. [***].

11.4 The costs of the corrective and preventative actions required to address the observations made by the Authority shall be borne by the Parties as follows:

(i) issues which are quality system violations or deficiencies or deficiencies of the Facility and Quality Systems which do not specifically relate to the Product or the Specific Equipment shall be timely corrected [***].

(ii) Any other modifications agreed upon by the Parties and which are specifically related to Product and are not due to system violations or deficiencies of the Facility and Quality Systems shall be corrected [***].

11.5 Where any audit carried out by OTL in accordance with this Clause 11 has identified findings, then the Parties shall discuss in good faith any reasonable corrective or preventative actions required to address any findings of any such audit and the cost allocation.

12. PAYMENTS

12.1 In consideration for the provision of Manufacturing Services, OTL shall pay to MolMed the applicable Manufacturing Fees set forth in **Schedule 1** and **Schedule 2**.

12.2 In consideration for the provision of Technology Transfer Services and Development Services, OTL shall pay to MolMed the applicable Service Fees set forth in **Schedule 3.** For the avoidance of doubt, any Service Fees payable with respect to Technology Transfer Services are payable in addition to the Technology Transfer Milestone Amounts set forth in **Schedule 3**.

12.3 For the granting of the exclusivity rights pursuant to Clause 2.1(e) MolMed shall invoice OTL for, and OTL shall pay, the amounts set out in **Schedule 4.**

12.4 Either party's cost responsibility is set forth in the Cost Responsibility Matrix (**Schedule 10**). All invoices to be issued by MolMed shall comply with the cost responsibility set forth in Schedule 10.

12.5 **Invoicing and payment.** Unless directed otherwise by OTL from time to time, all invoices to be issued by MolMed pursuant to this Agreement shall be sent to [***], MolMed shall ensure that each such invoice must include the following details:

- company letterhead in pdf format;
- bank details;

- PO details;
- contact name and contact number;
- invoice date and invoice number;
- reference of the Clause of this Agreement and or Schedule to which the invoice relates; and
- payment terms and currency, with reference to the relevant contract Clause.

a) OTL shall pay invoices issued by MolMed in accordance with this Agreement within [***] days from the date of receipt of invoice.

b) Payment by OTL of an invoice received from MolMed shall not constitute any admission or acceptance by OTL in relation to the performance or otherwise by MolMed of its obligations under this Agreement.

c) Interest may be charged on undisputed overdue payments at an annual interest rate of [***] that is effective on the due date of the payment (or on the next Business Day if the due date is not a Business Day), such interest to be pro-rated for the number of days from the date upon which payment of such sum became due until payment thereof in full together with such interest, provided, however, that in no event shall such rate exceed the maximum legal annual interest rate. The payment of such interest shall not limit a Party from exercising any other rights it may have as a consequence of the lateness of any payment.

d) All payments due from a Party (the **Payor**) to the other Party (the **Payee**) under this Agreement shall be paid in euros (€) by wire transfer to a euro (€) bank account designated in writing by the Payee from time to time.

e) Costs incurred or revenues received or payments due in currencies other than euros (€) shall first be calculated in the relevant foreign currency and then converted to euros (€) against the currency in question using the currency exchange rates that are used to convert foreign currency into Euros within the Payor's financial statements.

12.6 **Taxes**

All amounts due under this Agreement shall be paid by the Payor exclusive of any Sales Tax (which, if applicable, shall be payable by the Payor in addition upon receipt of a valid Sales Tax invoice).

All amounts due under this Agreement shall be paid in full without deduction for any applicable taxes, levies, imposts, duties and fees of whatever nature imposed by or under the authority of any government or public authority, except for tax legally required to be withheld. If a law or regulation of any country of the Territory requires withholding of taxes of any type, levies or other charges with respect to any amounts payable hereunder to Payee, Payor shall promptly pay such tax, levy, or charge for or on behalf of Payee to the proper governmental authority and shall furnish Payee with proof of such withholding or similar tax in a form in accordance with the relevant taxation authority as evidence of such payment. Payor shall have the right to deduct any such tax, levy or charge actually paid from payment due to Payee or be promptly reimbursed by Payee if no further payments are due to Payee. Payor agrees to assist Payee in claiming exemption from such deductions or withholdings under double taxation or similar agreement or treaty from time to time in force and in minimising the amount required to be so withheld or deducted and in obtaining a repayment of tax withheld or deducted.

12.7 **Invoicing Disputes**

If any part of an amount payable under an invoice prepared by MolMed is subject to a good faith dispute between OTL and MolMed:

1. OTL shall pay to MolMed all amounts not disputed in good faith by OTL and all Sales Tax due on any undisputed amount in accordance with Clause 12.5(a);

2. OTL shall notify MolMed, within [***] Business Days after the date of receipt by OTL of the relevant invoice, of any disputed amounts and shall, as soon as reasonably practicable after it has notified MolMed, describe in reasonable detail OTL's reasons for disputing each amount; and

3. the Parties shall seek to reach settlement of the items that are the subject of the dispute in accordance with the dispute resolution procedure in Clause 19.

4. When any dispute regarding an invoice is resolved, OTL shall pay any sum which is agreed or determined to be payable by OTL to MolMed (whether that sum is the amount originally invoiced or a reduced amount) together with any Sales Tax due within [***] Business Days after the date of resolution of that dispute provided that the new due date is not earlier than the original invoice due date in which case the original invoice due date still applies.

13. CONFIDENTIALITY

13.1 Confidentiality; Exceptions

Except to the extent expressly authorised by this Agreement (including authorisation by any licence granted under this Agreement) or otherwise agreed in writing, the Parties agree that the Receiving Party (the **Receiving Party**) shall keep confidential and shall not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the **Disclosing Party**) or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement including trade secrets, know-how, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to a Party's past, present and future marketing, financial, business, and research and development activities of the Disclosing Party hereunder (collectively, **Confidential Information**), except to the extent that it can be established by the Receiving Party that such Confidential Information:

i. was in the lawful knowledge and possession of the Receiving Party prior to the time it was disclosed to, or learned by, the Receiving Party, or was otherwise developed independently by the Receiving Party, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party;

ii. was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party;

iii. became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party in breach of this Agreement; or

iv. was disclosed to the Receiving Party, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party not to disclose such information to others.

For the avoidance of doubt but not limited to, (i) Arising OTL IPR, OTL Materials, OTL Background IPR and Arising Specific OTL IPR shall be considered the Confidential Information of OTL; ii) and MolMed Background IPR, MolMed Enablement Know How, MolMed Non-Enablement Know How and Molmed New IPR shall be considered the Confidential Information of MolMed (ii) nothing in this Clause 13 shall prevent a Party from exercising its rights pursuant to any licence granted to it under Clause 3.

13.2 Authorised Disclosure

To the extent it is necessary or appropriate to fulfil its obligations or exercise its rights under this Agreement, a Receiving Party may disclose such Confidential Information of the Disclosing Party as it is otherwise obliged under Clause 13.1:

a) to its Affiliates, and to its and their (whether actual or potential) directors, employees, sublicensees, consultants and subcontractors, on a need-to-know basis and on the condition that such Persons, and their employees and agents, agree in writing to keep the Confidential Information confidential for the same time periods and to the same extent as such Receiving Party is required to keep such Confidential Information confidential;

b) to government agencies and Regulatory Authorities to the extent that such disclosure is necessary or reasonably useful to progress the activities to be conducted hereunder; or

c) in prosecuting or defending litigation or in establishing rights or enforcing obligations under this Agreement or in complying with Applicable Law, court or administrative orders, the rules of any relevant stock exchange or similar governing body; provided, however, it shall to the extent permitted by the Applicable Law:

   i. give reasonable advance notice to the Disclosing Party of such disclosure requirement, to the extent practicable;

   ii. provide a copy of the proposed disclosure to the Disclosing Party;

   iii. only disclose Confidential Information of the Disclosing Party to the extent necessary for the performance of the Services and its obligations under this Agreement; and

   iv. at the request of the Disclosing Party, use Commercially Reasonable Endeavours to secure confidential treatment of such Confidential Information required to be disclosed.

All Confidential Information shall remain identified as the Disclosing Party's Confidential Information. In any circumstance where a Receiving Party is permitted to disclose Confidential Information of the Disclosing Party in accordance with Clause13.2, the Receiving Party shall remain fully responsible for any failure by any Person who receives the Confidential Information pursuant to those Clauses to treat such Confidential Information as confidential as required under this Clause 13.

13.3 Market Abuse Provisions.

a) The Parties are listed companies on stock exchanges and are therefore subject to the relevant laws and regulations provisions they are required to adhere to (Market Abuse Provisions). Both Parties undertake to comply with the provisions set forth in the Market Abuse Provisions to the extent applicable in connection with this Agreement.

b) Furthermore, OTL agrees that it will, to the extent such dealing is prohibited by applicable law, not use the content of Confidential Information, to deal in any securities of MolMed or in any derivative products related thereto or to encourage another person or entity so to deal. MolMed agrees that it will also, not use content of OTL Confidential Information, to deal in any securities of OTL or in any derivative products related thereto or to encourage another person or entity so to deal.

c) Notwithstanding the foregoing, it is further understood that both Parties hereby undertake not to (and shall ensure that its employees, agent and consultants to which have been provided by the Party with Confidential Information), directly or indirectly, by any means, without the prior consent of the other Party, acquire, agree to acquire, propose, seek or offer to acquire, or facilitate the acquisition or ownership of, any securities of the other Party, any warrant or option to purchase such securities, any security convertible into any such securities, or any right to acquire such securities ultimately.

d) In the case of communication of inside information to third parties who are not bound by a confidentiality agreement, the Party aware of this undertakes to immediately inform the affected Party.

e) Both Parties acknowledge that in the event of dissemination or unauthorized use of inside information, criminal and administrative penalties will apply (included those provided for under Articles 184 of the legislative decree).

13.4 Press Release; Disclosure of Agreement

a) After the Effective Date, either Party shall be permitted to make an announcement concerning this Agreement in the form at as mutually agreed on.

b) Either Party shall be entitled to use the other's name for promotion, publicity, marketing or advertising purpose, provided that the relevant section of the promotional material has been submitted to the other party for approval providing at least [***] business days notice from date of receipt in writing to the JOC members for review and approved in writing by the other Party. In the event that the submitting Party has not received any answer [***] business days from date of receipt of written notification, the promotional material shall be considered approved. OTL shall use its best effort, to include in any publication a statement to recognize the contribution of MolMed in respect to the Services.

c) Except to the extent set out in Clause 13.4(a) above or required by law, neither Party shall issue any press release or public disclosure concerning this Agreement, the subject matter hereof or the Parties' activities hereunder, or any results or data arising hereunder (where MolMed intends to disclose), except with the other Party's prior written consent with respect to the specific press release or disclosure proposed to be issued or released. The Parties agree to consult with each other reasonably and in good faith with respect to the text and timing of any such press releases and disclosures prior to the issuance thereof, and a Party may not unreasonably withhold consent to such releases and disclosures, and shall give due consideration to any reasonable comments by the other Party relating to such releases and disclosures, including where applicable subject matter for which confidential treatment may be sought. Where Confidential Information is present within any such releases or disclosures, the owner of the Confidential Information shall have the sole discretion to remove such Confidential Information from the intended release. For the avoidance of doubt with regards to any press release or public disclosure relating to results or data arising hereunder, OTL is not required to obtain MolMed's prior written consent to the specific press release or disclosure, provided that such publications do not include MolMed Confidential Information.

13.5 Remedies

Each Party shall be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Clause 13.

14. REPRESENTATIONS AND WARRANTIES

14.1 Representations and Warranties of Both Parties

Each Party hereby represents, warrants and covenants to the other Party, as of the Effective Date, that:

i. such Party is duly organised, validly existing and in good standing under the laws of the jurisdiction of its incorporation and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

ii. such Party has taken all necessary action on its part to authorise the execution and delivery of this Agreement and the performance of its obligations hereunder;

iii. this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid, binding obligation, enforceable against it in accordance with the terms hereof;

iv. the execution, delivery and performance of this Agreement by such Party does not conflict with or does not result in a breach of any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, nor violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

v. all employees and officers (other than administrative and non-technical personnel) of such Party and its Affiliates involved in the Services and other activities to be conducted pursuant to this Agreement have executed agreements requiring assignment to such Party or its Affiliates of all inventions made during the course of and as a result of their association with such Party or its Affiliates and obligating the individual to maintain as confidential the Confidential Information of such Party and its Affiliates;

vi. it has not taken any action that would in any way prevent it from granting the rights granted to the other Party under this Agreement and, to the best of its knowledge, it has the right to grant to the other Party the rights granted by it under this Agreement; and

vii. it is not aware on the Effective Date of any action, suit, inquiry or investigation instituted by any Third Party against it that questions or threatens the validity of this Agreement.

14.2 IPR Representations and Warranties

14.2.1 MolMed hereby represents, warrants and covenants to OTL, as of the Effective Date, that:

a) MolMed owns and has the right to grant all rights and licences it purports to grant to OTL under this Agreement (including the MolMed Enablement Licence);

b) so far as it is aware, the exercise by OTL of its rights under the MolMed Enablement Licence will not infringe or misappropriate the Intellectual Property Rights of any Third Party;

c) MolMed has not granted as of the Effective Date any right or licence to any Third Party relating to any MolMed Enablement Know-How or any MolMed Enablement Patent that would conflict or interfere with any of the rights or licences granted to OTL hereunder; and

d) there is no claim or litigation pending or, so far as it is aware, threatened, concerning any actual or alleged infringement or misappropriation of any Third Party's Intellectual Property Rights as a result of MolMed's provision of the Services or any services materially equivalent to the Services.

14.2.2 OTL hereby represents, warrants and covenants to MolMed, as of the Effective Date, that:

a) OTL owns and has the right to grant all rights and licences it purports to grant to MolMed under this Agreement (including the OTL Background IPR and the OTL License IPR, as well as OTL Materials, Specific Equipment, supplied, transferred or to be supplied or transferred to MolMed by OTL to perform the Services);

b) so far as it is aware as of the Effective Date, the exercise by MolMed of its rights under the OTL Background IPR and the OTL License IPR will not infringe or misappropriate the Intellectual Property Rights of any Third Party;

c) so far as it is aware, there is no claim or litigation pending or threatened in writing, concerning any actual or alleged infringement or misappropriation of any Third Party's Intellectual Property Rights as a result of MolMed's provision of the Services or any services materially equivalent to the Services.

14.3 Service Representations and Warranties of MolMed

14.3.1 MolMed hereby represents, warrants and covenants to OTL that:

a) all Services shall be performed in accordance with best practices and in a good and workmanlike fashion, with all due speed, care, skill and diligence, and using efficiently the resources necessary to provide the Services;

b) all Services shall be carried out i) in accordance with this Agreement and any applicable Quality Agreement; and ii) in accordance with Applicable Law and current industry standard codes of practice;

c) all of its personnel (and any personnel of its Subcontractors) engaged in the provision of any Services are suitably qualified to perform those Services; and

d) it has obtained or will maintain in force all necessary Manufacturing Licences and other applicable licenses and permits prior to the provision of Services and in sufficient time to enable MolMed to duly perform the Services in compliance with this Agreement and Applicable Law.

14.3.2 OTL hereby represents, warrants and covenants to MolMed, as of the Effective Date, thatit has obtained and shall obtain all Product Licences.

14.4 Manufacturing Representations and Warranties of MolMed

MolMed hereby represents, warrants and covenants to OTL that:

a) Subject to Clause 5 of Schedule 1 and Clause 5 of Schedule 2, each Product supplied hereunder [***];

b) each Product shall be Manufactured, quality controlled and packed in accordance with cGMP, the Quality Agreement, Applicable Laws and (to the extent applicable) EUTCD; and

c) it will convey good title to each Product supplied hereunder.

14.5 Limitation on Warranties

(a) MolMed extends no warranty whatsoever that: [***].

(b) The Parties acknowledge and agree that the warranties set forth in this Clause 14, together with any warranties expressly set out in this Agreement are their exclusive warranties with respect to Products and the Services. Except as otherwise expressly set forth in this Agreement, neither Party makes any other warranties or condition with respect to the product or the process, express or implied, and specifically disclaims the implied warranties and condition of merchantability, non-infringement and fitness for a particular purpose.

(c) MolMed shall not be liable for any non-compliance of any Product with the warranties expressly provided in this Agreement to the extent such non-compliance arises directly out of any act or omission of OTL, any Affiliate of OTL or any OTL Nominated User or its officers, directors, employees, agents and representatives, including without limitation any incorrect or misleading instruction, notice, document, or communication originating from OTL, any Affiliate of OTL or any OTL Nominated User.

15. INDEMNIFICATION; INSURANCE; LIMITATION OF LIABILITY

15.1 Indemnification by MolMed

MolMed shall defend, indemnify and hold harmless OTL and its Affiliates, and its or their respective directors, officers, employees, subcontractors and agents, from and against any and all liabilities, damages, losses, costs and expenses including the reasonable fees of attorneys and other professionals (collectively, **Losses**), arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands (**Third Party Claims**) based upon:

i. any Third Party personal injury, illness or death, or loss or damage to Third Party property arising from the supply of any Product that does not conform to the relevant Specifications, subject to Section 5 of Schedule 1 and Section 5 of Schedule 2, as at the date of the Availability Notice;

ii. any breach of Applicable Law by MolMed in the performance of the Services or its other obligations under this Agreement;

iii. any gross negligence or wilful misconduct of MolMed, its Affiliates or any of their respective directors, officers, employees, subcontractors and agents with respect to the performance of this Agreement (including any breach of any representation or warranty made by MolMed caused by such gross negligence or wilful misconduct);

iv. the cost of any recall of the Product where and to the extent that OTL can duly demonstrate that the Product is affected by Latent Defect resulting from MolMed Fault, and

v. any infringement of any Third Party's Intellectual Property Rights arising from the i) knowingly incorporation of any intellectual property that is not owned by, or otherwise licensable by MolMed in the performance of the Services without the prior written consent of OTL; or (iii) the use of MolMed Enablement Know How and MolMed Information provided such use is i) in connection with the performance of the Services and is otherwise in accordance with the terms of this Agreement, or ii) is related to MolMed Enablement Know How and MolMed Information incorporated into the Deliverable.

vi. except, in each case, to the extent that the Losses in question resulted from the gross negligence or wilful misconduct of OTL, or its Affiliate(s) or its or their respective directors, officers, employees, subcontractors and agents or the use by MolMed of OTL Materials, Critical Material, OTL Information or OTL Background IPR.

15.2 Indemnification by OTL

OTL shall defend, indemnify and hold harmless MolMed and its Affiliates, and its or their respective directors, officers, employees, subcontractors and agents, from and against any and all Losses arising out of or resulting from any and all Third Party Claims based upon:

i. any Third Party personal injury, illness or death, or loss or damage to Third Party property arising from the handling or use of any Product which at Availability Notice conformed to the relevant Specifications. Where handling and use includes, without limitation handling, processing, distributing, marketing, sale, administering (whether for clinical or commercial purposes);

ii. any breach of Applicable Law by OTL in the performance of its obligations under this Agreement;

iii. any gross negligence or wilful misconduct of OTL, its Affiliates or any of their respective directors, officers, employees, subcontractors and agents with respect to the performance of this Agreement (including any breach of any representation or warranty made by OTL caused by such gross negligence or wilful misconduct); and

iv. any infringement of any Third Party's Intellectual Property Rights arising from the use by MolMed of any OTL Material, OTL Information or OTL Background IPR licensed to MolMed for use in the course of performing the Services, provided such use is in connection with the performance of the Services and is otherwise in accordance with the terms of this Agreement,

except, in each case, to the extent that the Losses in question resulted from the gross negligence or wilful misconduct of MolMed, or its Affiliate(s) or its or their respective directors, officers, employees, subcontractors and agents.

15.3 Conduct of Third Party Claims

In the event that a Party (an **Indemnitee**) entitled to indemnification under Clause 15.1 or 15.2 is seeking such indemnification, such Indemnitee shall (a) inform, in writing, the indemnifying Party of the Third Party Claim as soon as reasonably practicable after such Indemnitee receives notice of such Third Party Claim, (b) permit the indemnifying Party to assume direction and control of the defence of the Third Party Claim (including the sole right to settle it at the sole discretion of the indemnifying Party, taking into consideration in good faith any reasonable concerns or objections raised by the Indemnitee; *provided that* such settlement does not impose any obligation on, or otherwise adversely affect, the Indemnitee or any of its Affiliates), (c) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defence of the Third Party Claim, and (d) undertake all reasonable steps to mitigate any loss, damage or expense with respect to the Third Party Claim.

15.4 Limitations on Liability

a) Neither Party shall have any liability to the other Party under or in connection with this Agreement to the extent that any breach or non-performance by such Party of any obligation, representation or warranty under this Agreement is due to the breach or non-performance by the other Party of any obligation, representation or warranty under this Agreement.

b) Subject to Clause15.4(d), neither Party shall be liable for: i) any indirect or consequential loss suffered or incurred by the other Party; or ii) any loss of profits (whether direct or indirect) suffered or incurred by the other Party.

c) Subject to Clause15.4(d), the aggregate liability of MolMed to OTL for Losses suffered or incurred by OTL in any Contract Year under or in connection with this Agreement, whether arising in tort (including negligence), for breach of contract or otherwise shall be limited to the [***].

d) Nothing in this Agreement shall exclude or limit either Party's liability: i) for death or personal injury caused by its negligence (or the negligence of its employees, agents or subcontractors); ii) for fraud or fraudulent misrepresentation; iii) for wilful misconduct or gross negligence; under the indemnities at Clauses 15.1 and 15.2; iv) for breach of confidentiality; v) breach of data protection; or vi) for any other liability to the extent that such liability may not be excluded or limited as a matter of law.

e) The Parties acknowledge and agree that MolMed is not involved in any clinical decision relating to the use of Drug Product or in the selection of patients for treatment by means of Drug Product. Without prejudice to Clause 15.1 and MolMed's obligations under this Agreement, MolMed shall have no liability under this Agreement in respect of any harm suffered by a patient treated with Drug Product that on Availability Notice complied in all respects with the requirements of this Agreement.

15.5 Insurance

Without limiting its responsibilities or liabilities hereunder, MolMed shall at its own expense effect and maintain full third party, public and product liability insurance that is sufficient with respect to its potential liabilities under this Agreement, and which at a minimum shall include the following insurance:

a)Without limiting its responsibilities or liabilities hereunder, MolMed shall at its own expense effect and maintain full third party, public and product liability insurance that is sufficient with respect to its potential liabilities under this Agreement, and which at a minimum shall include the following insurance:

1. Public Liability insurance in respect of MolMed's liability for loss of or damage to property including property of OTL and its customers, against liability in respect of death

and injury, and in respect of MolMed's liability for all claims for injury, loss or damage arising out of any defect in the Deliverables provided in the performance of this Agreement for the sum of not less than [***] for any one occurrence and per calendar year; and

2. employer's Liability insurance at the required statutory levels.

b) Such insurance shall be maintained throughout the Term with one or more reputable insurance companies and MolMed shall, if and whenever requested, provide OTL with satisfactory evidence of such insurance being in force.

c) MolMed shall at its own expense effect and maintain insurance in respect of injury, loss or damage arising out of any errors, acts or omissions in the performance of professional duties of MolMed under this Agreement.

16. ANTI-BRIBERY AND ANTI-CORRUPTION

(a) Each Party agrees that it shall comply fully at all times with all Applicable Laws, including, without limitation, anti-corruption laws, and that it has not, and covenants that it will not, in connection with the performance of this Agreement, directly or indirectly, make, promise, authorise, ratify or offer to make, or take any act in furtherance of any payment or transfer of anything of value for the purpose of influencing, inducing or rewarding any act, omission or decision to secure an improper advantage; or improperly assisting it or either Party in obtaining or retaining business, or in any way with the purpose or effect of public or commercial bribery, and warrants that it has taken reasonable measures to prevent subcontractors, agents or any other third parties, subject to its control or determining influence, from doing so. For the avoidance of doubt this includes facilitating payments, which are unofficial, improper, small payments or gifts offered or made to government officials to secure or expediate a routine or necessary action to which we are legally entitled.

(b) Either Party shall be entitled to terminate this Agreement immediately on written notice to the other Party, if that Party fails to perform any of its obligations in accordance with this Clause 16 ("**Breaching Party**"). The Breaching Party shall have no claim against the other Party for compensation for any loss of whatever nature by virtue of the termination of this Agreement in accordance with this Clause 16.

17. LABOUR RIGHTS

(a) Each Party represents and warrants to the other Party, to the best of its knowledge, that in connection with this Agreement, it respects the human rights of its staff and does not employ child labour, forced labour, unsafe working conditions, or cruel or abusive disciplinary practices in the workplace and that it does not discriminate against any workers on any ground (including race, religion, disability, gender, sexual orientation or gender identity); and that it pays each employee at least the minimum wage, provides each employee with all legally mandated benefits, and complies with Applicable Laws on working hours and employment rights in the countries in which it operates.

(b) Each Party shall be respectful of its employees right to freedom of association and each Party shall encourage compliance with these standards by any supplier of goods or services that it uses in performing its obligations or exercising its rights under this Agreement.

18. TERM AND TERMINATION

18.1 Term

a) This Agreement shall become effective as of the Effective Date and shall remain in full force and effect for a period of five (5) years or until such time as it is terminated pursuant to the other provisions of this Clause 18.

b) During the [***], the Joint Operating Committee shall meet to conduct a general review of the Parties' relationship under this Agreement and discuss whether any amendments should be made to Agreement and to the Manufacturing Fees and the Service Fees.

c) In case of agreement, the amended version of the Agreement shall remain in full force for [***] provided [***], the Joint Operating Committee shall meet to conduct a general review of the Parties' relationship under this Agreement and discuss whether any amendments should be made to Agreement and to the Manufacturing Fees and the Service Fees and if no such agreement is reached the procedure set forth in let d) shall apply.

d) If no such agreement is reached, the term of the Agreement shall be deemed to be extended [***] and the Manufacturing Fees and the Service Fee in force at the time of the review shall be [***] provided that [***].

18.2 Termination

a) Termination for Cause

Each Party (the **Non-Breaching Party**) shall have the right, without prejudice to its other rights or remedies, to terminate this Agreement upon [***] days' written notice to the other Party (the "**Breaching Party")** if the Breaching Party is in material breach of this Agreement (being a single event or a series of events which are together a material breach), provided that, if the Breaching Party has remedied that breach within the [***] day notice period, this Agreement shall not terminate and shall continue in full force and effect.

The following shall represent a non-exhaustive list of material breaches of either Party: a) failure by OTL to timely pay the undisputed amount due with respect to [***] b) MolMed failure to comply with its obligations under [***].

Without prejudice to any other rights or remedies available under this Agreement or at Applicable Law, MolMed may forthwith terminate this Agreement upon written notice pursuant to Article 1456 of the Italian Civil Code in any of the following circumstances, to be also deemed as material breaches:

(a) OTL uses the MolMed Enablement Know-How outside the scope of this Agreement and/or not in compliance with the material limitations prescribed hereunder

(c) OTL materially fails to comply with the confidentiality duties under Clause 13;

Without prejudice to any other rights or remedies available under this Agreement or at Applicable Law, OTL may forthwith terminate this Agreement upon written notice pursuant to Article 1456 of the Italian Civil Code in any of the following circumstances, to be also deemed as material breaches:

(a) MolMed uses the Arising OTL IPR and the OTL Background IPR outside the scope of this Agreement and/or not in compliance with the material limitations prescribed hereunder;

(b) MolMed materially fails to comply with the confidentiality duties under Clause 13.

OTL shall have the right, without prejudice to its other rights or remedies, to terminate this Agreement with immediate effect if MolMed fails to keep or loses its license to manufacture Product or MolMed receives an unsatisfactory audit report from Regulatory Authorities which OTL can demonstrate i) places MolMed at risk of losing its manufacturing license and ii) that have a significant material impact on OTL ability to perform its clinical trial or commercial supply of Drug Product.

b) Termination for Insolvency

Each Party (the **First Party**) shall have the right, without prejudice to its other rights or remedies, to terminate this Agreement by written notice to the other Party (the **Second Party**) if any bona fides step, process, application, filing in court, order, proceeding, notice or appointment is taken or made by or in respect of the First Party for a moratorium, composition, compromise or arrangement with creditors, administration, liquidation (other than for the purposes of amalgamation or reconstruction), dissolution, receivership (administrative or otherwise), distress or execution, or the First Party becomes insolvent or is deemed unable to pay its debts as they fall due, or anything analogous to the foregoing occurs in any applicable jurisdiction.

In circumstances whereby MolMed is the Second Party, OTL shall have the right, without prejudice to its other rights or remedies, to enter MolMed premises to collect and obtain its OTL Materials and/or Products.

c) Termination for Default Change of Control of MolMed

OTL shall have the right, without prejudice to its other rights or remedies, to terminate this Agreement with immediate effect by written notice to MolMed if there is a Default Change of Control of MolMed.

d) Termination by OTL for Convenience

OTL may terminate this Agreement (either in whole or with respect to any one or more Indication) for convenience at any time provided that it gives MolMed written notice of such termination at least twelve (12) months prior to the date on which such termination would take effect.

e) Termination by MolMed for Convenience

MolMed may terminate this Agreement for convenience at any time provided that it gives OTL written notice of such termination at least twenty-four (24) months prior to the date on which such termination would take effect. MolMed may not give notice to terminate for convenience through the first twenty four (24) month period in accordance with Clause 18.1(a).

18.3 **Consequences of Expiry or Termination**

a) Cessation of Obligations

Save as expressly provided in this Clause 18.3 upon expiry or termination of this Agreement for any reason each Party's rights and obligations under this Agreement shall immediately terminate.

MolMed shall fulfill any Product Orders (i) received from OTL prior to OTL or MolMed receiving a termination notice hereunder, or during the termination notice period, provided that the estimate date of completion does not exceed the expiry or termination date.

b) Post-Termination Licence Grants

Upon termination of this Agreement for any reason:

i) the licences granted by [***] shall automatically and immediately terminate; and

ii) the licence granted to [***] shall continue in full force and effect;

iii) the licences granted by [***] shall continue in full force and effect for [***] at the time of termination;

iv) the MolMed Enablement Licence [***] with respect to the [***] Field if the termination is by OTL pursuant to Clause 18.2(a) (Termination for Cause);

v) the MolMed Enablement Licence [***] with respect to the [***] Field if the termination is for any reason not covered by sub paragraph iv) above.

c) Termination Payments

If this Agreement is terminated:

a) by OTL pursuant to Clauses 18.2(a) (**<u>Termination by OTL for Cause</u>**) or or by MolMed pursuant to Clauses 18.2 (e) (**<u>Termination by MolMed for convenience</u>**), or by OTL pursuant to Clause 18.2 (c) (**<u>Termination for Default Change Control of MolMed</u>**) MolMed shall reimburse OTL an amount equal to:

A. [***];

B. [***]; and

C. [***].

D. OTL shall pay MolMed [***].

b) by OTL pursuant to Clause d) (**<u>Termination by OTL for Convenience</u>**) or by MolMed pursuant to Clause d) (**<u>Termination by MolMed for Cause</u>**):

A. OTL shall not be entitled to [***]; and

B. OTL shall [***] and;

C. OTL shall [***].

d) Technology Transfer

Upon termination of this Agreement for any reason, MolMed shall transfer and deliver to OTL (or the applicable TT Nominee) such Relevant Know-How as is reasonably required by OTL (or its applicable TT Nominee) in order for OTL (or the TT Nominees, as applicable) to assume responsibility for the provision of services equivalent to the Services being provided by MolMed to OTL as at the date of termination, in accordance with the technology transfer protocol to be agreed between the Parties. OTL shall [***]. In the event of termination [***].

e) Return of Confidential Information

Subject to Clause18.3(f) and (g), the Receiving Party, at its own cost and expense, shall within [***] Business Days after the date of termination return or otherwise destroy (at the election of the other Party) the Confidential Information (including all such documents containing such Confidential Information) of the Disclosing Party, provided that the Receiving Party may retain one (1) copy of the Disclosing Party's Confidential Information in accordance with Clause 13 solely for the purpose of monitoring compliance with the terms of this Agreement. The foregoing shall not require the Receiving Party to access and remove any Confidential Information of the Disclosing Party located in any archived back up electronic mail tapes so long as such archived backup electronic mail tapes are not accessible in the ordinary course of business of the Receiving Party and provided that such archived back-up electronic tapes shall continue to be the Confidential Information of the Receiving Party and shall remain subject to the terms of Clause 13.

f) Right to Retain MolMed Enablement Know-How

The Parties agree that, due to OTL's perpetual, irrevocable rights under the MolMed Enablement Licence, nothing in Clause 16.3(f) shall require OTL to return any MolMed Enablement Know-How to MolMed.

g) Right to Retain Arising General OTL IPR

The Parties agree that nothing in Clause 18.3 shall require MolMed to return any Arising General OTL IPR to OTL.

18.4 **Accrued Rights; Surviving Provisions of this Agreement**

a) Termination of this Agreement for any reason shall be without prejudice to any rights that shall have accrued to the benefit of any Party prior to such termination including, [***] and any and all damages arising from any breach hereunder. Termination of the Agreement shall not relieve any Party from obligations which are expressly indicated to survive termination of this Agreement.

The provisions of Clauses

[***]

, shall survive the termination of this Agreement for any reason, in accordance with their respective terms and conditions, and for the duration stated, and where no duration is stated, shall survive indefinitely. Any provision of this Agreement that expressly or by implication is intended to come into or continue in force on or after termination or expiry of this agreement shall remain in full force and effect.

19. DISPUTE RESOLUTION

19.1 Any dispute, claim or controversy arising out of, relating to or having connection with this Agreement (including any dispute as to its existence, validity, interpretation, performance, breach or termination or the consequences of its nullity and any dispute relating to any non-contractual obligations arising out of or in connection with it) (each, a **Dispute**), shall be resolved in accordance with this Clause 19 and Clause 20.1.

19.2 Any Dispute shall be referred for resolution by either Party to the Joint Operating Committee for resolution and, depending on the timing of the next Joint Operating Committee meeting, the Parties shall determine (acting reasonably and in good faith) whether it is necessary to call an emergency meeting of the Joint Operating Committee to consider the Dispute. If the Dispute cannot be resolved by the Joint Operating Committee within [***] Business Days after the Dispute has been referred to it for resolution, either Party may give notice to the other Party in writing that a Dispute has arisen (**Dispute Notice**).

19.3 Within [***] Business Days after the date of receipt of the Dispute Notice, each Party shall refer the Dispute to a relevant senior executive that it nominates for the purposes of resolving the Dispute. If the Dispute is not resolved by agreement in writing between the Parties [***] Business Days after the date of receipt of the Dispute Notice, the Dispute may at either Party's request be referred to the tribunal of Milan in accordance with Clause 20.1

19.4 This Clause 19 and Clause 20.1 does not limit either Party's right to seek interim relief against the other Party (such as an injunction) through the Italian courts to protect its rights and interests, or to enforce the obligations of the other Party.

19.5 Notwithstanding the foregoing, this Clause 19 shall not apply to any dispute in relation to which Clause 5.2 (non-conforming batch disagreements) of Schedule 1 and Clause 5.2 non-conforming batch disagreements) of Schedule 2 applies.

20. MISCELLANEOUS

20.1 Governing Law & Jurisdiction

This Agreement and any non-contractual obligations arising out of or in connection with it shall be governed by and construed in accordance with the laws of Italy without giving effect to any choice of law or conflict of law provisions. The Parties consent to the exclusive jurisdiction and venue in the tribunal of Milan.

20.2 Amendments

Any amendment of this Agreement shall not be binding on the Parties unless set out in writing, expressed to amend this Agreement and signed by authorised representatives of each of the Parties.

20.3 Human Biological Sample Management

Each Party represents and warrants that it complies with and will continue to comply with all Applicable Laws, regulations, codes of practice and guidance relating to the collection, storage, use and disposal of Human Biological Samples and Data (the **Regulatory Requirements**) for use in the performance of the Services hereunder and that the appropriate consent at the material time (as required by the Regulatory Requirements) has on all occasions been given and will be obtained in the future in respect of all Human Biological Samples and Data to be collected, transferred, stored, used and disposed of after the date of this Agreement in connection with such Services.

20.4 Privacy

In order to fulfil their obligations pursuant to this Agreement and, in particular, to (i) carry out any activity provided by law or regulations, (ii) handle bookkeeping, orders, invoicing and any disputes and (iii) store documents as required by Applicable Law, the Parties confirm the receipt of adequate privacy notice with reference to their respective employees' personal data treatment, if any.

20.5 **Non solicitation** During the term of this Agreement and for a period of [***] thereafter, each of the Parties agrees not to seek to induce or solicit any employee of the other party or its Affiliates to discontinue his or her employment with the other party or its Affiliate in order to become an employee or an independent contractor of the soliciting party or its Affiliate; provided, however, that neither party shall be in violation of this Section 20.5 as a result of making a general solicitation for employees or independent contractors, or hiring any person who independently responds to any such general solicitation. For the avoidance of doubt, the publication of an advertisement shall not constitute solicitation or inducement.

20.6 **Ethical Standards and Human Rights**

a) Unless otherwise required or prohibited by law, MolMed warrants that so far as it is aware in relation to the provision of Services under the terms of this Agreement:

i. it does not employ engage or otherwise use any child labour in circumstances such that the tasks performed by any such child labour could reasonably be foreseen to cause either physical or emotional impairment to the development of such child;

ii. it does not use forced labour in any form (prison, indentured, bonded or otherwise) and its employees are not required to lodge papers or deposits on starting work;

iii. it provides a safe and healthy workplace, presenting no immediate hazards to its employees. Any housing provided by MolMed to its employees is safe for habitation. MolMed provides access to clean water, food, and emergency healthcare to its employees in the event of accidents or incidents at MolMed's workplace;

iv. it does not discriminate against any employees on any ground (including race, religion, disability or gender);

v. it does not engage in or support the use of corporal punishment, mental, physical, sexual or verbal abuse and does not use cruel or abusive disciplinary practices in the workplace;

vi. it pays each employee at least the minimum wage, or a fair representation of the prevailing industry wage, (whichever is the higher) and provides each employee with all legally mandated benefits;

vii. it complies with the laws on working hours and employment rights in the countries in which it operates; and

viii. it is respectful of its employees right to join and form independent trade unions and freedom of association.

b) MolMed agrees that it is responsible for controlling its own supply chain and that it shall encourage compliance with ethical standards and human rights by any supplier of goods and services that are used by MolMed when performing its obligations under this Agreement.

c) MolMed shall ensure that it has ethical and human rights policies and an appropriate complaints procedure to deal with any breaches of such policies. In the case of any complaints, MolMed shall report the alleged complaint and proposed remedy to OTL.

d) OTL reserves the right upon reasonable notice (unless inspection is for cause, in which case no notice shall be necessary) to enter upon MolMed's premises to monitor compliance by MolMed of the warranties set out in Clause 14 and MolMed shall, subject to compliance with Applicable Law, furnish OTL with any relevant documents requested by OTL in relation thereto.

OTL acknowledges that MolMed has adopted a Code of Ethics available on MolMed's website, which MolMed will adhere to.

MolMed acknowledges that OTL has adopted a Code of Ethics available on OTL's website, which OTL will adhere to.

20.7 **Assignment and Subcontracting**

a) Subject to Clause 20.7 (b) and 20.7 (c), neither Party may assign, transfer or otherwise dispose of any of its rights or subcontract, transfer (including by way of novation) or otherwise dispose of any of its obligations under this Agreement without the prior written consent of the other Party.

b) Nothing in this Agreement shall prevent or restrict OTL from assigning, transferring, novating or otherwise disposing of any of its rights or from subcontracting, transferring, novating or otherwise disposing of any of its obligations under this Agreement to an Affiliate of OTL or to any Person acquiring the whole or any part of OTL's business or assets to which this Agreement relates.

c) MolMed shall not subcontract any part of its obligations under this Agreement without OTL's prior written consent, which shall not be unreasonably withheld or delayed.

d) MolMed shall be responsible for all acts and omissions of the Subcontractors as fully as if they were the acts and omissions of MolMed or its employees or agents. MolMed shall be OTL's sole point of contact for the performance of MolMed's obligations under this Agreement.

e) OTL acknowledges that MolMed shall not be responsible for any delay arising from any Approved Subcontractor Provided that MolMed shall promptly notify OTL in writing of delay, the cause and the likely duration of the delay and use all reasonable endeavours to limit the effect of that delay.

It is clearly understood that [***]. Notwithstanding anything to the contrary under this Agreement [***].

20.8 **Force Majeure**

Neither Party shall be liable to the other Party for any delay or non-performance of its obligations under this Agreement arising directly from any event beyond its reasonable control including, without limitation: shortage of materials, governmental act, act of terrorism, war, fire, earthquake, flood, or other natural disasters, embargo, riot, sabotage, strike (other than of its own employees), explosion or civil commotion lack or failure of transport facilities, currency restrictions, or events caused by reason of laws, regulations or orders by any government, governmental agency or instrumentality, or failure of third party delivery (which are not related to facts, events or conditions that would also be a breach by such Party of its obligation under this Agreement) (**Force Majeure Event**).

a) If a Force Majeure Event occurs, the affected Party shall:

- promptly notify the other Party in writing of the cause of the delay or non-performance and the likely duration of the delay or non-performance; and
- use all reasonable endeavours to limit the effect of that delay or non-performance on the other Party.

b) In case of a Force Majeure Event, the time for performance required by a Party under this Agreement shall be extended for any period during which the performance is prevented by the event. However, the other Party may terminate this Agreement by notice if such an event prevents performance continuously for more than [***] days.

20.8 **Notices:**

All requests, notices, approvals consents (collectively and individually referred to as “Notice”) to be given under this Agreement shall be in writing and, unless otherwise expressly provided in this Agreement, shall be served personally, by pre-paid registered post or courier with return receipt requested to the address of the intended addressee as set out hereunder or to such other address as may be notified to the other Party in writing:

If to OTL: Orchard Therapeutics (Europe) Limited 108 Cannon Street, London, EC4N 6EU [***]	If to MolMed MolMed S.p.A. Via Olgettina 58 20132 Milano [***]

This Clause shall not apply in relation to the service of any claim form, notice, order, judgment or other document relating to or in connection with any proceedings, suit or claim arising out of or in connection with this Agreement.

20.9 **Costs and Expenses**

Except as otherwise provided in this Agreement, each Party shall pay the costs and expenses incurred by it in connection with the entering into and completion of this Agreement.

20.10 **Waiver**

(a) The rights of each Party under this Agreement: i) may be exercised as often as necessary; ii) unless otherwise expressly provided in this Agreement, are cumulative and not exclusive of rights or remedies provided by law; and iii) may be waived only in writing and specifically.

(b) Delay in exercise or non-exercise of any such right is not a waiver of that right.

(c) A waiver (whether express or implied) by one of the Parties of any of the provisions of this Agreement or of any breach of or default by the other Party in performing any of those provisions shall not constitute a continuing waiver and that waiver shall not prevent the waiving Party from subsequently enforcing any of the provisions of this Agreement not waived or from acting on any subsequent breach of or default by the other Party under any of the provisions of this Agreement.

20.11 **Severability**

If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties shall negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such provision in any other jurisdiction. The invalidity or unenforceability of any term of or any right arising pursuant to this Agreement shall not adversely affect the validity or enforceability of the remaining terms and rights.

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY “[***]”, HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

20.12 **Entire Agreement**

a) This Agreement, together with the Schedules and Annexes hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties hereto with respect to the subject matter hereof and supersede and terminate all prior agreements and understanding between the Parties with respect to the subject matter hereof.

b) Subject to Clause 20.12 (c), each party acknowledges that in entering into this Agreement it has not relied on any covenant, warranty, representation, collateral contract or other assurance, either oral or written, (other than as set forth herein and therein) made by or on behalf of the other Party before the Effective Date. Each Party waives all rights and remedies which, but for this Clause 18, might otherwise be available to it in respect of any such covenant, warranty, representation, collateral contract or other assurance.

c) Nothing in Clause 20.12 (b) limits or excludes any liability for fraud.

20.13 **Independent Contractors**

Nothing in this Agreement shall be deemed to constitute a partnership between the Parties, nor constitute either Party the agent of the other Party for any purpose.

20.14 **Counterparts**

This Agreement may be executed in any number of counterparts, all of which, taken together, shall constitute one and the same agreement, and any Party (including any duly authorised representative of a Party) may enter into this Agreement by executing a counterpart.

20.15 Brexit

If the United Kingdom withdraws from the EU and such withdrawal have a material effect on the activities contemplated under this Agreement, the rights or obligations of either Party hereunder (including fiscal and economic effects or excessive burden) the Parties shall negotiate in good faith an adjustment or amendment to the terms hereof if necessary to preserve each Party’s rights hereunder as such rights were reasonably contemplated by the Parties as of the Effective Date. For clarity, a withdrawal from the EU by the United Kingdom, shall not constitute a Force Majeure Event.

The following Annexes shall form integral part of this Supply Agreement:

Schedule 1 – Manufacturing Services (Viral Vector)

Schedule 2 – Manufacturing Services (Drug product)

Schedule 3 – Development Services & Technology Transfer Services

Schedule 4 – Exclusive Transduction Suite

Schedule 5 - OTL Materials and Critical Material

Schedule 6 – Specific Equipment

Schedule 7 - Deliverables

Schedule 8 - Fixed Fees

Schedule 9 – Non Enablement Know- How

Schedule 10 – Cost Responsibility Matrix

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorised representatives as of the Effective Date.

SIGNATORIES

ORCHARD THERAPEUTICS (EUROPE) Limited

By: /s/ John Ilett

Name: John Ilett

Title Chief Legal Officer

MOLMED S.p.A.

By: /s/ Riccardo Palmisano

Name: Riccardo Palmisano

Title: CEO

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 1 – Manufacturing Services (Viral Vector)

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 2 – Manufacturing Services (Drug product)

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 3 – Development Services & Technology Transfer Services

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 4 – Exclusive Transduction Suite

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 5 - OTL Materials and Critical Material

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 6 – Specific Equipmentd

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 7 – Deliverables

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY “[***]”, HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 8 – Fixed Fees

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 9 – Non Enablement Know- How

[***]

CERTAIN IDENTIFIED INFORMATION CONTAINED IN THIS EXHIBIT, MARKED BY "[***]", HAS BEEN EXCLUDED BECAUSE IT IS BOTH (i) NOT MATERIAL AND (ii) WOULD LIKELY CAUSE COMPETITIVE HARM TO THE COMPANY IF PUBLICLY DISCLOSED.

Schedule 10 – Cost Responsibility Matrix

[***]

Exhibit 31.1

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

I, Bobby Gaspar, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: August 6, 2020

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

Exhibit 31.2

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

I, Frank E. Thomas, certify that:

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

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

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

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

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

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

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

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

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

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

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

Date: August 6, 2020

By: /s/ Frank E. Thomas
Frank E. Thomas
President and Chief Operating Officer

Exhibit 32.1

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

In connection with the Quarterly Report of Orchard Therapeutics plc(the “Company”) on Form 10-Q for the period ending June 30, 2020 as filed with the Securities and Exchange Commission on the date hereof (the “Report”), each of the undersigned officers does hereby certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

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

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

Date: August 6, 2020

By: /s/ Bobby Gaspar
Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: August 6, 2020

By: /s/ Frank E. Thomas
Frank E. Thomas
President and Chief Operating Officer
(Principal Financial Officer and Principal Accounting Officer)