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, 2022

OR

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

For the transition period from to

Commission File Number: 001-38722

ORCHARD THERAPEUTICS PLC

(Exact Name of Registrant as Specified in its Charter)

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

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

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

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

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

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

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

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

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

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

As of July 29, 2022, the registrant had 126,458,312 ordinary shares, nominal value £0.10 per share, outstanding.

Summary of the Material Risks Associated with Our Business

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

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

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

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- the timing, scope or likelihood of regulatory submissions, filings and approvals;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the market opportunity for and size of the patient populations for Libmeldy (OTL-200) and our product candidates, if approved, for commercial use;
- the implementation of our business model and our strategic plans for our business;
- our plans and ability to build out our commercial infrastructure, including our ability to successfully identify patients and market and sell Libmeldy in Europe and any of our product candidates for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of Libmeldy and any of our product candidates, if approved, including reimbursement for patients treated in a country where they are not resident;
- the adequacy, scalability and commercial viability of our manufacturing capacity, methods and processes, including those of our manufacturing partners, and plans for future development;
- the rate and degree of market acceptance and clinical utility of our commercial products and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships;
- our ability to obtain additional funding for our operations;
- the impact of the COVID-19 global pandemic on our business operations, including clinical trials, regulatory strategy, and the operations of our third-party manufacturers, suppliers and partners;
- the scope of protection we and our licensors are able to establish and maintain for intellectual property rights covering our commercial products and product candidates;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our ability to attract and retain qualified employees and key personnel;
- our ability to contract with third party suppliers, clinical sites and manufacturers and their ability to perform adequately;
- our projected financial condition, including the sufficiency of our cash, cash equivalents and investments to fund operations in future periods and future liquidity, working capital and capital requirements;
- our ability to comply with the listing requirements of The Nasdaq Stock Market;
- the impact of inflation on our business, results of operations or financial condition;
- the impact of geopolitical events, including the ongoing conflict between Russia and Ukraine; and

- other risks and uncertainties, including those listed under the caption “Item 1A. Risk Factors” in this 10-Q.

You should refer to the section titled “*Item 1A. Risk Factors*” in this 10-Q for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot be assured that the forward-looking statements in this 10-Q will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, these statements should not be regarded as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this 10-Q and the documents that we reference in this 10-Q and have filed as exhibits to this 10-Q completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

Item 1. Financial Statements.

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

	June 30, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 53,470	$ 55,912
Marketable securities	117,421	164,195
Accounts receivable	4,129	1,480
Prepaid expenses and other current assets	19,077	23,011
Research and development tax credit receivable	11,226	30,723
Total current assets	205,323	275,321
Operating lease right-of-use-assets	25,455	24,316
Property and equipment, net	5,733	4,767
Restricted cash	4,266	4,266
Intangible assets, net	3,736	4,149
Research and development tax credit receivable	3,950	—
Other assets	10,696	9,590
Total assets	$ 259,159	$ 322,409
Liabilities and Shareholders' Equity		
Current liabilities:		
Accounts payable	$ 8,802	$ 10,008
Accrued expenses and other current liabilities	26,286	24,318
Deferred revenue, current	1,147	346
Operating lease liabilities	6,670	7,335
Notes payable, current	5,500	786
Total current liabilities	48,405	42,793
Notes payable, long-term	27,539	32,086
Deferred revenue, net of current portion	10,291	12,519
Operating lease liabilities, net of current portion	20,183	19,278
Other long-term liabilities	6,469	5,783
Total liabilities	112,887	112,459
Commitments and contingencies (see Note 13)		
Shareholders' equity:		
Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 of shares at June 30, 2022 and December 31, 2021, respectively; 126,436,213 and 125,674,095 shares issued and outstanding at June 30, 2022 and December 31, 2021, respectively.	16,353	16,253
Additional paid-in capital	949,325	940,675
Accumulated other comprehensive income	26,030	3,246
Accumulated deficit	(845,436)	(750,224)
Total shareholders' equity	146,272	209,950
Total liabilities and shareholders' equity	$ 259,159	$ 322,409

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,	
	2022	2021	2022	2021
Product revenue, net	$ 3,781	$ —	$ 8,840	$ —
Collaboration revenue	587	—	1,052	—
Total revenue	4,368	—	9,892	—
Costs and operating expenses:				
Cost of product revenue	1,122	—	2,693	—
Research and development	21,965	21,750	50,199	42,785
Selling, general and administrative	13,730	14,263	27,029	28,314
Total costs and operating expenses	36,817	36,013	79,921	71,099
Loss from operations	(32,449)	(36,013)	(70,029)	(71,099)
Other income (expense):				
Interest income	213	113	282	284
Interest expense	(672)	(593)	(1,347)	(1,131)
Other income (expense), net	(18,227)	634	(24,279)	1,992
Total other income (expense), net	(18,686)	154	(25,344)	1,145
Loss before income taxes	(51,135)	(35,859)	(95,373)	(69,954)
Income tax (expense) benefit	219	(750)	161	(1,837)
Net loss attributable to ordinary shareholders	$ (50,916)	$ (36,609)	$ (95,212)	$ (71,791)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (0.40)	$ (0.29)	$ (0.75)	$ (0.60)
Weighted average ordinary shares outstanding, basic and diluted	127,854,596	125,952,834	127,775,132	120,421,781
Other comprehensive income (loss):				
Foreign currency translation adjustment	17,450	(374)	23,045	(438)
Unrealized loss on marketable securities	(1)	(8)	(261)	(121)
Total other comprehensive income (loss):	17,449	(382)	22,784	(559)
Total comprehensive loss	$ (33,467)	$ (36,991)	$ (72,428)	$ (72,350)

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,	
	2022	2021
Cash flows from operating activities:		
Net loss attributable to ordinary shareholders	$ (95,212)	$ (71,791)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	1,366	1,003
Share-based compensation	8,616	11,809
Non-cash interest expense	186	200
Amortization of provision on loss contract	(276)	(814)
Amortization of premium on marketable securities	189	761
Unrealized foreign currency and other non-cash adjustments	25,092	7,657
Changes in operating assets and liabilities:		
Accounts receivable	(2,997)	893
Research and development tax credit receivable	13,289	(7,800)
Prepaid expenses, other current assets and other assets	769	(543)
Operating leases, right-of-use assets	2,777	2,518
Accounts payable, accrued expenses and other current liabilities	4,251	(14,341)
Deferred revenue	(138)	—
Operating lease liabilities	(3,887)	(4,846)
Net cash used in operating activities	(45,975)	(75,294)
Cash flows from investing activities:		
Proceeds from sales and maturities of marketable securities	97,214	133,511
Purchases of marketable securities	(50,891)	(166,966)
Purchases of property and equipment	(1,572)	(935)
Receipt of funds from construction deposit	—	199
Net cash provided by (used in) investing activities	44,751	(34,191)
Cash flows from financing activities:		
Proceeds from employee equity plans, net of taxes withheld	137	2,836
Proceeds from the issuance of ordinary shares in private placement	—	150,000
Payment of placement agent fees and offering costs	—	(6,355)
Proceeds from modification of credit facility, net of debt issuance costs paid	—	7,375
Net cash provided by financing activities	137	153,856
Effect of exchange rate changes on cash, cash equivalents, and restricted cash	(1,355)	423
Net increase (decrease) in cash, cash equivalents and restricted cash	(2,442)	44,794
Cash, cash equivalents, and restricted cash, beginning of period	60,178	59,401
Cash, cash equivalents, and restricted cash, end of period	$ 57,736	$ 104,195
Supplemental disclosure of non-cash activities		
Property and equipment and intangible assets included in accounts payable and accrued expenses	$ 1,046	$ 2,860
Supplemental disclosure of cash flow information:		
Lease assets obtained in exchange for new operating lease liabilities, net	4,912	386
Non-cash adjustments to operating lease right-of-use assets and liabilities	530	—
Cash paid for interest	1,153	931

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

ORCHARD THERAPEUTICS PLC

Condensed Consolidated Statements of Shareholders' Equity

(In thousands, except share amounts)

(unaudited)

	Ordinary Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total
	Shares	Amount				
Balance at December 31, 2021	125,674,095	$ 16,253	$ 940,675	$ 3,246	$ (750,224)	$ 209,950
Share-based compensation expense	—	—	4,660	—	—	4,660
Exercise of share options	222,381	28	(29)	—	—	(1)
Vesting of restricted stock units, net of shares withheld for taxes	3,217	1	(4)	—	—	(3)
Ordinary shares issued as part of a consulting agreement	5,252	1	—	—	—	1
Foreign currency translation	—	—	—	5,595	—	5,595
Unrealized loss on available for sale debt securities	—	—	—	(260)	—	(260)
Net loss attributable to ordinary shareholders	—	—	—	—	(44,296)	(44,296)
Balance at March 31, 2022	125,904,945	16,283	945,302	8,581	(794,520)	175,646
Share-based compensation expense	—	—	3,956	—	—	3,956
Exercise of share options	175,153	24	(23)	—	—	1
Issuance of ESPP shares	356,115	46	90	—	—	136
Foreign currency translation	—	—	—	17,450	—	17,450
Unrealized loss on available for sale debt securities	—	—	—	(1)	—	(1)
Net loss attributable to ordinary shareholders	—	—	—	—	(50,916)	(50,916)
Balance at June 30, 2022	126,436,213	$ 16,353	$ 949,325	$ 26,030	$ (845,436)	$ 146,272

	Ordinary Shares		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total
	Shares	Amount				
Balance at December 31, 2020	98,283,603	$ 12,507	$ 771,194	$ 373	$ (605,640)	$ 178,434
Share-based compensation expense	—	—	6,268	—	—	6,268
Exercise of share options	1,319,493	172	2,650	—	—	2,822
Vesting of restricted stock units, net of shares withheld for taxes	45,746	6	(302)	—	—	(296)
Sale of ordinary shares and non-voting ordinary shares, net of issuance costs of $6,289	24,115,755	3,310	140,401	—	—	143,711
Foreign currency translation	—	—	—	(64)	—	(64)
Unrealized loss on available for sale debt securities	—	—	—	(113)	—	(113)
Net loss attributable to ordinary shareholders	—	—	—	—	(35,182)	(35,182)
Balance at March 31, 2021	123,764,597	15,995	920,211	196	(640,822)	295,580
Share-based compensation expense	—	—	5,541	—	—	5,541
Exercise of share options	15,725	2	7	—	—	9
Issuance of ESPP shares	102,775	13	288	—	—	301
Issuance costs associated with sale of voting and non-voting ordinary shares	—	—	(66)	—	—	(66)
Foreign currency translation	—	—	—	(374)	—	(374)
Unrealized loss on available for sale debt securities	—	—	—	(8)	—	(8)
Net loss attributable to ordinary shareholders	—	—	—	—	(36,609)	(36,609)
Balance at June 30, 2021	123,883,097	$ 16,010	$ 925,981	$ (186)	$ (677,431)	$ 264,374

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

1. Nature of the Business

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

The Company is a public limited company incorporated pursuant to the laws of England and Wales. The Company has American Depositary Shares ("ADSs") registered with the U.S. Securities and Exchange Commission (the "SEC") 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.

On February 9, 2021, the Company issued and sold (i) 20,900,321 ordinary shares, nominal value £0.10 per share, at a purchase price of $6.22 per share (the "Purchase Price"), which was the closing sale price of the Company's ADSs on the Nasdaq Global Select Market on February 4, 2021, and (ii) 3,215,434 non-voting ordinary shares, nominal value £0.10 per share, at the Purchase Price (together (i) and (ii) the "Private Placement"). The Private Placement resulted in net proceeds to the Company of $143.6 million after deducting placement agent fees of $6.0 million and other issuance costs of $0.4 million. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement entered into between the Company and the purchasers named therein on February 4, 2021.

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

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

Through June 30, 2022, the Company funded its operations primarily with proceeds from the sale of equity securities, including ADSs in the Company's initial public offering ("IPO") and follow-on offering, ordinary shares in the private placement, and convertible preferred shares. The Company has also financed its operations through proceeds from the Company's senior term facilities agreement with MidCap Financial (Ireland) Limited, research grants from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from the Company's collaboration agreement and share purchase agreement with Pharming Group N.V., and proceeds associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program. The Company has incurred recurring losses since its inception. As of June 30, 2022, the Company had an accumulated deficit of $845.4 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, 2022 of $170.9 million will be sufficient to fund its operations, capital expenditures and debt service payments for at least the next twelve months.

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

2. Basis of Presentation and Summary of Significant Accounting Policies

Basis of presentation

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

The accompanying unaudited condensed consolidated interim financial statements should be read in conjunction with the audited consolidated financial statements and accompanying notes included in the Company's Annual Report on Form 10-K filed with the SEC on March 30, 2022 (the "Annual Report"). The condensed consolidated balance sheet as of December 31, 2021 was derived from audited consolidated financial statements included in the Company's Annual Report but does not include all disclosures required by U.S. GAAP.

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

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

Use of estimates

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

Foreign currency

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. dollar are translated into U.S. dollars using period-end exchange rates for assets and liabilities, historical exchange rates for shareholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in shareholders' equity. Foreign currency transaction gains and losses arising from transactions denominated in currencies other than the functional currency of the individual entity are included in other income (expense), net in the results of operations. The Company recorded realized and unrealized foreign currency transaction losses of $24.3 million for the six months ended June 30, 2022 and realized and unrealized foreign currency transaction gains of $2.0 million for the six months ended June 30, 2021, which is included in other income (expense), net in the condensed consolidated statements of operations and comprehensive loss.

Cash and cash equivalents

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

Marketable securities

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

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

United Kingdom research and development tax credit

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

Each reporting period, management evaluates which tax relief programs the Company is expected to be eligible for and records a reduction to research and development expense for the portion of the expense that it expects to qualify under the programs, that it plans to submit a claim for, and it has reasonable assurance that the amount will ultimately be realized. Based on criteria established by HM Revenue and Customs ("HMRC"), management of the Company expects a proportion of expenditures being undertaken in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for the research and development tax relief programs for the year ended December 31, 2022. The Company expects when it files its claim for the years ended December 31, 2021 and 2022, it will qualify under the SME regime.

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Balance at beginning of period	$ 16,649	$ 21,044	$ 30,723	$ 17,344
Recognition of credit claims as offset to research and development expense	1,764	4,246	5,101	7,800
Receipt of credit claims	(1,916)	—	(18,390)	—
Foreign currency translation	(1,321)	81	(2,258)	227
Balance at end of period	$ 15,176	$ 25,371	$ 15,176	$ 25,371

As of June 30, 2022, the Company's tax incentive receivable from the UK government was $15.2 million, of which $11.2 million was classified as current. As of December 31, 2021, the Company's tax incentive receivable from the UK government was $30.7 million, all of which was classified as current.

Restricted cash and construction deposits

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as restricted cash on the Company's condensed consolidated balance sheets. The Company has an outstanding letter of credit for $3.0 million associated with a lease and is required to hold this amount in a standalone bank account, as of June 30, 2022 and December 31, 2021. 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, 2022 and December 31, 2021.

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

	June 30, 2022	December 31, 2021
Cash and cash equivalents	$ 53,470	$ 55,912
Restricted cash	4,266	4,266
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 57,736	$ 60,178

The Company has $7.9 million in an escrow account associated with construction on the Fremont facility, for which the Company has ceased construction and build-out and subleased to a third-party. Subject to the terms of the lease and reduction provisions, this amount will be returned to the Company upon qualifying construction expenditure or will be returned in late 2022 to the extent construction expenses have not been incurred. The Company deposited $10.0 million into the account in the first quarter of 2020 and has received $2.1 million in receipts from the escrow funds for costs incurred to date. Of the $7.9 million remaining in the escrow account, the entire balance is classified within prepaid expenses in the condensed consolidated balance sheets based on the timing of when the Company expects funds to be returned from the escrow agent.

Accounts receivable

Accounts receivable arise from product revenue and amounts due from the Company's collaboration partners and have standard payment terms that generally require payment within 30 to 90 days. The amount from product revenue represents amounts due from distributors in Europe, which are recorded net of reserves for trade discounts and allowances, and other incentives to the extent such amounts are payable to the customer by the Company. The Company monitors economic conditions to identify facts or circumstances that may indicate that its receivables are at risk of collection. The Company provides reserves against accounts receivable for estimated losses, if any, that may result from a customer's inability to pay based on the composition of its accounts receivable, current economic conditions, and historical credit loss activity. Amounts determined to be uncollectible are charged or written-off against the reserve. During the three and six months ended June 30, 2022, the Company did not record any expected credit losses related to outstanding accounts receivable.

Product revenue, net

Libmeldy

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

The Company recognizes revenue when control of promised goods is transferred to a customer at an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods. Control of the product transfers upon infusion of the product. To determine revenue recognition, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the Company satisfies the performance obligations. The Company only applies the five-step model to contracts when collectability of the consideration to which we are entitled in exchange for the goods the Company transfers to the customer is determined to be probable. In certain regions of Europe and the Middle East, the Company utilizes distributors to act in an agent capacity including for patient identification and other related functions. The Company is exclusively responsible for product fulfillment and retains inventory risk and pricing discretion of the product. Evaluation of these key indicators support the assertion that the Company maintains control over the product prior to delivery to the patient. The Company has concluded that it is the principal in these transactions and records the associated revenue on a gross basis.

Amounts are recorded as accounts receivable when the right to the consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. The Company expenses incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that would have been recognized is one year or less or the amount is immaterial. As of June 30, 2022, the Company has not capitalized any costs to obtain contracts.

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

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

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

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

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

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

Strimvelis

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

Disaggregated Product Revenue Disclosures

The Company disaggregates revenue from contracts with customers by product type as it believes this presentation best depicts how the nature, amount, timing and uncertainty of the Company's revenue and cash flows are affected by economic factors, as shown below (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Libmeldy	$ 3,145	$ —	$ 8,204	$ —
Strimvelis	636	—	636	—
	$ 3,781	$ —	$ 8,840	$ —

During the three months ended June 30, 2022, the Company did not record any product revenue reserves. During the six months ended June 30, 2022, Libmeldy included product revenue reserves primarily related to governmental rebates of $1.2 million.

Strimvelis loss provision

As part of its transaction with Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD (together, “GSK”), 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 12). Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company initially recorded a liability associated with the loss contract of $18.4 million in 2018. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with Strimvelis and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a reduction in research and development expense. The Company has made an estimate of the expected future losses associated with Strimvelis and adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of the future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for updates to estimates of potential future losses.

The following table below outlines the changes to the Strimvelis loss provision for the three and six months ended June 30, 2022 and 2021 (amounts in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Balance at beginning of period	$ 3,057	$ 4,076	$ 3,419	$ 4,482
Amortization of loss provision	—	(368)	(276)	(814)
Foreign currency translation	(230)	28	(316)	68
Balance at end of period	$ 2,827	$ 3,736	$ 2,827	$ 3,736

Of the balance as of June 30, 2022 noted in the table above, $0.9 million is classified as current, and $2.0 million is classified as non-current.

Net loss per share

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

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

	As of June 30,	
	2022	2021
Share options	13,894,428	12,625,435
Unvested performance-based restricted share units	500,989	692,668
	14,395,417	13,318,103

Recently adopted accounting pronouncements

In November 2021, the FASB issued ASU No. 2020-10, *Government Assistance (Topic 832):* Disclosures by Business Entities about Government Assistance, which requires increased transparency in the disclosures about government assistant in the notes to the financial statements. This ASU is effective for the Company beginning January 1, 2022, and interim periods within that year, with early adoption permitted. The Company adopted and applied the amendments of this ASU to its disclosures. The application of this ASU did not have a material impact on its financial position, results of operations or cash flows.

3. Fair value measurements and marketable securities

The following tables present information about the Company's financial assets that have been measured at fair value as of June 30, 2022 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 and six months ended June 30, 2022 and 2021, there were no transfers between Level 1 and Level 2 financial assets.

The following table summarizes the Company's cash equivalents and marketable securities as of June 30, 2022 (amounts in thousands):

	Fair Value Measurements at June 30, 2022 Using:			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 14,739	$ —	$ —	$ 14,739
Commercial paper	—	8,991	—	8,991
Total cash equivalents	$ 14,739	$ 8,991	$ —	$ 23,730
Marketable securities				
Corporate bonds	$ —	$ 41,436	$ —	$ 41,436
Commercial paper	—	75,985	—	75,985
Total marketable securities	$ —	$ 117,421	$ —	$ 117,421
Total	$ 14,739	$ 126,412	$ —	$ 141,151

The following table summarizes the Company's cash equivalents and marketable securities as of December 31, 2021 (amounts in thousands):

	Fair Value Measurements at December 31, 2021 Using:			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 21,085	$ —	$ —	$ 21,085
Corporate bonds	—	7,321	—	7,321
Commercial paper	—	13,198	—	13,198
Total cash equivalents	$ 21,085	$ 20,519	$ —	$ 41,604
Marketable securities				
Corporate bonds	$ —	$ 94,794	$ —	$ 94,794
Commercial paper		69,401	—	69,401
Total marketable securities	$ —	$ 164,195	$ —	$ 164,195
Total	$ 21,085	$ 184,714	$ —	$ 205,799

The carrying amount reflected on 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 securities

The following table summarizes the Company's level 2 cash equivalents and marketable securities as of June 30, 2022 (amounts in thousands):

	June 30, 2022				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
Corporate bonds	$ 41,652	$ —	$ (216)	$ —	$ 41,436
Commercial paper	85,188	—	(212)	—	84,976
Total	$ 126,840	$ —	$ (428)	$ —	$ 126,412

The following table summarizes the Company's level 2 cash equivalents and marketable securities as of December 31, 2021 (amounts in thousands):

	December 31, 2021				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
Corporate bonds	$ 102,224	$ —	$ (109)	$ —	$ 102,115
Commercial paper	82,657	—	(58)	—	82,599
Total	$ 184,881	$ —	$ (167)	$ —	$ 184,714

The following table summarizes the Company's debt securities by contractual maturity, as of June 30, 2022 and December 31, 2021 (amounts in thousands):

	June 30, 2022	December 31, 2021
Maturities in one year or less	$ 122,192	$ 172,575
Maturities between one year and three years	4,220	12,139
Total	$ 126,412	$ 184,714

4. Prepaid expenses and other current assets

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

	June 30, 2022	December 31, 2021
Prepaid external research and development expenses	$ 2,271	$ 2,438
Inventories	1,919	2,016
Other prepayments	3,579	6,128
VAT receivable	1,122	1,169
Construction deposit - current	7,909	7,909
Non-trade receivables	2,277	3,351
Total prepaid expenses and other current assets	$ 19,077	$ 23,011

5. Intangible assets, net

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

	June 30, 2022			December 31, 2021		
	Cost	Accumulated Amortization	Net	Cost	Accumulated Amortization	Net
License intangibles	$ 4,075	$ (339)	$ 3,736	$ 4,329	$ (180)	$ 4,149
Total	$ 4,075	$ (339)	$ 3,736	$ 4,329	$ (180)	$ 4,149

License intangibles consist of capitalized milestone payments or accruals of payments the Company has deemed probable upon receiving regulatory approval of Libmeldy in the EU. The license intangibles are being amortized on a straight-line basis over the remaining useful life of the related patents of approximately twelve years. For the three and six months ended June 30, 2022, amortization of intangible assets totaled $0.1 million and $0.2 million, respectively. For the three and six months ended June 30, 2021, amortization of intangible assets was nil. The effect of foreign currency translation on the net carrying value of intangible assets for each of the three and six months ended June 30, 2022 was $0.2 million. The following table summarizes the estimated future amortization for intangible assets for the next five years and thereafter (amounts in thousands):

Year Ending December 31,	
2022 (Remaining six months)	$ 183
2023	354
2024	354
2025	354
2026	354
Thereafter	2,137
Total	$ 3,736

6. Accrued expenses and other current liabilities

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

	June 30, 2022	December 31, 2021
Accrued external research and development expenses	$ 10,405	$ 9,273
Accrued payroll and related expenses	7,095	8,521
Accrued other	8,786	6,524
Total accrued expenses and other current liabilities	$ 26,286	$ 24,318

7. Notes payable

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

In May 2021, the Company amended and restated the Original Credit Facility (the "Amended Credit Facility"). Under the Amended Credit Facility, the Lenders agreed to make term loans available to the Company in the aggregate amount of $100.0 million, including increasing the principal on the initial term loan to $33.0 million, from $25.0 million. To date, the Company has borrowed $33.0 million under the amended initial term loan. The remaining $67.0 million under the Amended Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a $33.0 million term loan available no earlier than July 1, 2022 and no later than July 1, 2023 upon certain regulatory approvals and evidence of the Company having $100.0 million in cash and cash equivalent investments; and the third term loan being a $34.0 million term loan available no earlier than July 1, 2023 and no later than July 1, 2024 upon evidence of the Company having $100.0 million in cash and cash equivalent investments and attaining a pre-specified trailing 12-month revenue target.

Each term loan under the Amended Credit Facility bears interest at an annual rate equal to 5.95% plus LIBOR. The Company is required to make interest only payments on the term loan for 18 months following the date of the Amended Credit Facility, unless the Company is eligible for the second tranche, in which case the Company may elect to make interest-only payments for 30 months following the date of the Amended Credit Facility. The term loans under to the Amended Credit Facility begin amortizing on either the 18-month or the 30-month anniversary of the Amended Credit Facility (as applicable), with equal monthly payments of principal plus interest to be made by the Company to the Lenders in consecutive monthly installments until the loan maturity date. In addition, a

final payment of 3.5% is due on the loan maturity date. The Company is accruing the final payment amount of $1.2 million associated with the first term loan of the Amended Credit Facility, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the loan maturity date.

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

Notes payable consist of the following (amounts in thousands):

	June 30, 2022	December 31, 2021
Notes payable, net of issuance costs	$ 32,712	$ 32,669
Less: current portion	(5,500)	(786)
Notes payable, net of current portion	27,212	31,883
Accretion related to final payment	327	203
Notes payable, long term	$ 27,539	$ 32,086

As of June 30, 2022, the estimated future principal payments due are as follows (amounts in thousands):

Year Ending December 31,	Aggregate Minimum Payments
2022 (Remaining six months)	$ 786
2023	9,429
2024	9,429
2025	9,429
2026	5,084
Total	34,157
Less: current portion	(5,500)
Less: unamortized portion of final payment	(828)
Less: unamortized debt issuance costs	(290)
Notes payable, long term	$ 27,539

During the three months ended June 30, 2022 and 2021, the Company recognized $0.7 million and $0.6 million of interest expense, respectively, related to the term loan. During the six months ended June 30, 2022 and 2021, the Company recognized $1.3 million and $1.1 million of interest expense, respectively, related to the term loan. The effective annual interest rate for the three and six months ended June 30, 2022 on the outstanding debt under the term loan was approximately 8.1%.

8. Share-based compensation

The Company maintains four equity compensation plans; the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"), the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "2018 Plan"), the 2018 Employee Share Purchase Plan (the "ESPP"), and the 2020 Inducement Equity Plan (the "Inducement Plan"). The board of directors has determined not to make any further awards under the 2016 plan following the Company's IPO. As of June 30, 2022, 4,576,090 shares remained available for issuance under the 2018 Plan, 721,500 shares remained available for issuance under the Inducement Plan, and 823,497 shares remained available for issuance under the ESPP.

Share option activity

The following table summarizes option activity under the plans for the six months ended June 30, 2022:

	Number of Options	Weighted Average Exercise Price
Outstanding at December 31, 2021	17,300,740	$ 6.57
Granted	3,165,732	0.56
Exercised	(397,534)	0.00
Forfeited	(2,845,240)	7.13
Outstanding at June 30, 2022	17,223,698	$ 5.52
Vested and expected to vest as of June 30, 2022	17,223,698	$ 5.52
Exercisable June 30, 2022	8,268,318	$ 6.84

The weighted-average grant date fair value of share options granted during the six months ended June 30, 2022 was $0.32 per share.

Restricted share units

Performance-based restricted share units

In April 2020, the Company granted 195,000 performance-based restricted share units restricted share units ("RSUs") with a total grant date fair value of $1.4 million to its Chief Executive Officer, Bobby Gaspar, M.D., Ph.D. The award vests on January 2, 2024 as to 1/3 of the award for each of the first three to occur of four milestones, if each such milestone is achieved by the Company on or before December 31, 2023 and Dr. Gaspar remains continuously employed with the Company through January 2, 2024. The milestones relate to achievement of specific clinical and regulatory milestones. No performance-based share unit performance conditions associated with this award were deemed probable and none vested during the three and six months ended June 30, 2022.

Time-based restricted share units

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

Restricted share unit activity

The following table summarizes award activity for the six months ended June 30, 2022:

	Performance-based RSUs	Time-based RSUs	Total RSUs	Weighted Average Grant Date Fair Value
Unvested and outstanding at December 31, 2021	195,000	123,333	318,333	$ 6.41
Granted	—	2,112,842	2,112,842	0.46
Vested	—	(6,667)	(6,667)	(5.98)
Forfeited	—	(71,800)	(71,800)	0.46
Unvested and outstanding at June 30, 2022	195,000	2,157,708	2,352,708	$ 0.67

Share-based compensation expense

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Research and development	$ 1,744	$ 2,135	$ 3,706	$ 5,011
General and administrative	2,212	3,406	4,910	6,798
	$ 3,956	$ 5,541	$ 8,616	$ 11,809

As of June 30, 2022, total unrecognized compensation cost related to unvested share options and time-based RSUs was approximately $24.3 million. This amount is expected to be recognized over a weighted average period of approximately 2.6 years. As of June 30, 2022, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $1.4 million, dependent upon achievement of the aforementioned milestones.

9. Restructuring charges

On March 30, 2022, the Company announced its commitment to focus on severe neurometabolic diseases and early research programs, and to discontinue its investment in and seek strategic alternatives for the Company's programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich syndrome ("WAS"), OTL-102 for treatment of X-linked chronic granulomatous disease ("X-CGD"), and Strimvelis for adenosine deaminase severe combined immunodeficiency ("ADA-SCID"). The Company recognized a one-time charge in the first half of 2022 of approximately $1.9 million, which relates to employee-related termination costs. For the six months ended June 30, 2022, approximately $1.6 million and $0.4 million is recognized in research and development expenses and selling, general, and administrative expenses, respectively, in the Company's condensed consolidated statements of operations and comprehensive loss. The balance of the restructuring accrual was included in accrued expenses and other current liabilities on the Company's condensed consolidated balance sheets. Activity for the three and six months ended June 30, 2022 is summarized as follows (amounts in thousands):

	Three Months Ended June 30, 2022	Six Months Ended June 30, 2022
Balance at beginning of period	$ 2,481	$ 6
Charged to expense	—	2,481
Non-cash adjustments and foreign currency translation	(554)	(554)
Payments made	(1,089)	(1,095)
Balance at end of period	$ 838	$ 838

10. License agreements

GSK asset purchase and license agreement

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

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

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. The Company will pay a flat mid-single digit percentage royalty on the annual net sales of Strimvelis. The Company will also pay tiered royalty rates at a percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at a percentage from the high single-digits to low double-digit for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition or through June 30, 2022 and are not included as part of consideration.

Telethon-OSR research and development collaboration and license agreements

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

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones, up to an aggregate of approximately €31.0 million ($32.4 million as of June 30, 2022). Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses of the collaboration programs.

In May 2019, the Company entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Company an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's *ex vivo* autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I, including the Hurler variant ("MPS-IH"). Under the terms of the agreement, Telethon-OSR received €15.0 million in upfront and milestone payments from the Company upon entering into the agreement, resulting in $17.2 million in in-process research and development expense. The Company is also required to pay up to €28.0 million ($29.3 million as of June 30, 2022) related to milestone payments contingent upon achievement of certain development, regulatory and commercial milestones. Additionally, the Company will be required to pay Telethon a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

Oxford BioMedica license, development and supply agreement

In November 2016, and amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica plc whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and whereby Oxford BioMedica will provide process development services ("Oxford BioMedica Development Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Development Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and fourth milestones were achieved, and the Company issued 150,826 ordinary shares. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million which was recorded to research and development expense. No milestones were met during the three and six months ended June 30, 2022. The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

11. Collaboration agreement with Pharming Group N.V.

Overview

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

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

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

Share Purchase Agreement

The Company also entered into a Share Purchase Agreement with Pharming on July 1, 2021 (the "SPA"), pursuant to which the Company issued 1,227,738 ordinary shares to Pharming for total consideration of $7.5 million. The consideration is payment for the fair value of ordinary shares with a fair value of $4.1 million plus a $3.4 million premium on the fair value of the Company's ordinary shares.

The "Collaboration Agreement" and the "SPA" are referred to together as the "Pharming Agreements."

Accounting Analysis

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 1,227,738 of the Company's ordinary shares as part of the SPA, and the license and collaboration agreement, which conveys the license and provides for the Company to provide research, development, manufacturing services for OTL-105. The Pharming Agreements were entered into concurrently as part of a single commercial objective, and the Company considers them a single arrangement for accounting purposes. The total upfront payments of $17.5 million comprises $4.1 million attributed to the equity sold to Pharming and $13.4 million attributed to the Collaboration Agreement. In determining the fair value of the common stock issued to Pharming as part of the SPA, the Company used an option pricing valuation model to take into consideration certain holding period restrictions on the shares. The fair value of the Company's common shares was considered a level 2 fair value measurement within the fair value hierarchy. The most significant assumptions within the model are the Company's stock price, the term of the restrictions and the stock price volatility, which is based upon historical volatility of the Company's stock. Based on the fair value adjustments made by management, the fair value of the shares issued was determined to be $4.1 million with the excess proceeds of $3.4 million being allocated to the Collaboration Agreement.

The Company recognizes revenue under ASC 606, *Revenue from Contracts with Customer*. The Company has concluded that the conveyance of the license for the HAE program and the provision of research, development, and manufacturing services for the HAE program represent a series of distinct services that are accounted for as a single performance obligation within the Collaboration Agreement. The Company determined that the transaction price includes: the non-refundable up-front payment of $10.0 million, the $3.4 million in premium associated with the SPA, and the variable consideration for estimated reimbursement payments at agreed upon contractual rates to be received from Pharming for the Company's on-going research, development, and manufacturing services. The potential future variable consideration associated with reimbursement for research, development, and manufacturing services provided by the Company to Pharming at agreed upon contractual rates is the only remaining unsatisfied performance obligation. The milestone payments included in the Collaboration Agreement are fully constrained, as a result of the uncertainty regarding whether any of the associated milestones will be achieved and therefore, the Company determined that it could not assert that it was probable that a significant reversal in the amount of cumulative revenue recognized will not occur. The total estimated cost of the research and development services reflect the nature of the services to be performed and the Company's best estimate of the length of time required to perform the services. The Company re-evaluates the transaction price as of the end of each reporting period.

The Company also considered the existence of any significant financing component within the Pharming Agreements given their upfront payment structure. Based upon this assessment, the Company concluded that the up-front payments were provided for valid business reasons and not for the purpose of providing financing. Accordingly, the Company has concluded that the upfront payment structure of the Pharming Agreements does not result in the existence of a significant financing component.

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

The following table summarizes collaboration revenue recognized in connection with the Company's performance under the Collaboration Agreement (amounts in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2022	2021	2022	2021
Reimbursement revenue	$ 515	$ —	$ 915	$ —
Upfront and milestone payment revenue	72	—	137	—
Total	$ 587	$ —	$ 1,052	$ —

The Company had $0.5 million and $0.8 million due from Pharming included in accounts receivable as of June 30, 2022 and December 31, 2021, respectively.

As of June 30, 2022, the Company had contract liabilities of $11.4 million, which is classified as either current or long-term deferred revenue in the condensed consolidated balance sheets based on the period over which this is expected to be recognized. The deferred revenue balance represents the portion of the upfront payments received that are partially unsatisfied as of June 30, 2022.

12. Income taxes

The Company recorded an income tax benefit of $0.2 million and income tax expense of $0.8 million for the three months ended June 30, 2022 and 2021, respectively. The Company recorded an income tax benefit of $0.2 million and income tax expense of $1.8 million for the six months ended June 30, 2022 and 2021, respectively. The Company records no income tax benefits for the net operating losses incurred in each period in the U.K due to the uncertainty regarding the realizability of the deferred tax asset. The Company's income tax relates to its subsidiaries in Europe and the U.S. The Company's income tax computed at its effective income tax rate for the three and six months ended June 30, 2022 differed from income taxes computed at the U.K. statutory tax rate primarily due to provision to return adjustments recorded for certain European subsidiaries, capitalization of research and experimental expenditures under the Internal Revenue Code Section 174, partially offset by an increase in the U.S. deduction for foreign derived intangible income and U.S. tax credits and share-based compensation. The Company's income tax computed at its effective income tax rate for the three and six months ended June 30, 2021 differed from income taxes computed at the U.K. statutory tax rate primarily due to share-based compensation shortfalls.

Effective for tax years beginning on or after January 1, 2022, research and experimental expenditures under Internal Revenue Code Section 174 must be capitalized over five years when performed in the U.S. and 15 years for research and experimental expenditures performed outside of the U.S.

13. Commitments and contingencies

Legal proceedings

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

Manufacturing and technology development master agreement with AGC Biologics

The Company is party to an Agreement with AGC Biologic S.p.A ("AGC") pursuant to which the Company is obligated to pay AGC for a minimum product manufacturing commitment, dedicated manufacturing and development resources, and for a lease component associated with the right of use of exclusive manufacturing suites within AGC's existing facilities. The following table outlines the current commitments associated with the agreement, as of June 30, 2022 (amounts in thousands):

Due in:	Product manufacturing commitments	Dedicated manufacturing and development resources	Exclusive transduction suites	Total remaining AGC commitment
2022 (Remaining six months)	$ 941	$ 2,899	$ —	$ 3,840
2023	1,883	5,508	2,092	9,483
2024	1,883	5,508	2,092	9,483
2025	941	2,754	1,046	4,741
Total manufacturing commitments	$ 5,648	$ 16,669	$ 5,230	$ 27,547

* Tabular disclosure above has been translated to U.S. Dollar, from Euro, using the period end exchange rate of €1.00 to $1.05.

Lease commitments

The Company leases office and laboratory space and has an embedded lease at AGC. During the quarter ended March 31, 2022, the Company entered into a new lease in the U.K. for a period of 120 months. As of June 30, 2022, total future minimum payments due under this lease amount to $8.7 million. Other than this new lease, there have been no material changes to the Company's lease commitments as reported in the Company's Annual Report on Form 10-K.

Compliance with Nasdaq Continued Listing Requirements

In April 2022, the Company received a letter from the Nasdaq Stock Market ("Nasdaq") stating that it was not in compliance with the minimum bid price requirement for continued listing on the Nasdaq Global Select Market because the closing bid price for the Company's ADSs was below $1.00 per share for 30 consecutive business days. The notice from Nasdaq has no immediate effect on the listing of the Company's ADSs, and the ADSs will continue to be listed on the Nasdaq Global Select Market under the symbol

“ORTX”. The Company have been afforded a 180-calendar day period, or until October 3, 2022, to regain compliance with the minimum bid price requirement. The continued listing standard will be met if the closing bid price of the Company’s ADSs is at least $1.00 per share for a minimum of ten consecutive business days during the 180-calendar day period. If the Company is not in compliance by October 3, 2022, the Company may be afforded a second 180-calendar day period to regain compliance if it meets certain requirements. The Company intends to monitor the closing bid price of its ADSs and it is currently evaluating its options for regaining compliance, which could include adjusting the ADS-to-ordinary share ratio.

14. 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 recoded expense of $0.5 million and $0.4 million in matching contributions for the three months ended June 30, 2022 and 2021, respectively. The Company recorded expense of $1.0 million and $0.9 million in matching contributions for the six months ended June 30, 2022 and 2021, respectively.

Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this Quarterly Report on Form 10-Q. Some of the information contained in this discussion and analysis and set forth elsewhere in this Quarterly Report on Form 10-Q, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in Part II—Item 1A of this Quarterly Report on Form 10-Q for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Business overview

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

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 in our IPO and follow-on offering, ordinary shares in our private placement, and convertible preferred shares. We have also financed our operations through proceeds from the Amended Credit Facility with MidCap Financial, research grants from CIRM, upfront payments from our collaboration agreement with Pharming Group N.V., and proceeds associated two UK research and development tax relief programs, the SME program and the RDEC program.

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

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

Our net losses were $95.2 million and $71.8 million for the six months ended June 30, 2022 and 2021, respectively. As of June 30, 2022, we had an accumulated deficit of $845.4 million. As of June 30, 2022, we had cash, cash equivalents and marketable securities of $170.9 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

On March 30, 2022, we announced that we would focus on severe neurometabolic diseases and early research programs and discontinue our investment in and seek strategic alternatives for our programs in rare primary immune deficiencies, including OTL-103 for treatment of WAS, OTL-102 for treatment of X-CGD and Strimvelis for ADA-SCID. In March 2022 we also approved a restructuring pursuant to which our workforce was reduced by approximately 30%. The reduction in force took place and was substantially completed in the second quarter of 2022.

On July 1, 2021, we announced a strategic collaboration with Pharming to research, develop, manufacture and commercialize OTL-105, an investigational *ex vivo* autologous HSC gene therapy for the treatment of hereditary angioedema (HAE), a life-threatening rare disorder that causes recurring swelling attacks in the face, throat, extremities and abdomen. Under the terms of the collaboration, Pharming was granted worldwide rights to OTL-105 and will be responsible for clinical development, regulatory filings and

commercialization of the investigational gene therapy, including associated costs. The Company will lead the completion of IND-enabling activities and oversee manufacturing of OTL-105 during preclinical and clinical development, which will be funded by Pharming. In addition, both the Company and Pharming will explore the application of non-toxic conditioning regimen for use with OTL-105 administration. The Company received an upfront payment of $17.5 million comprising $10.0 million in cash and a $7.5 million equity investment from Pharming at a premium to the Company's then recent share price, resulting in the issuance of 1,227,738 ordinary shares subject to resale restrictions. The Company is also eligible to receive up to $189.5 million in development, regulatory and sales milestones as well as mid-single to low double-digit percentage royalty payments on future worldwide sales.

On May 28, 2021, we notified UCL Business Plc ("UCLB") and The Regents of the University of California ("UCLA") that we would terminate the license relating to OTL-101 for ADA-SCID, which was granted to us pursuant to the license agreement, dated February 6, 2016, among us, UCLB and UCLA, as amended (the "License Agreement"). On July 29, 2022, we finalized an agreement regarding the termination of the license ("Termination Agreement") with UCLA and UCLB. In connection with the Termination Agreement, the license, certain intellectual property rights, know-how, materials, data and regulatory filings, documents and approvals, including those developed or funded by the Company, have reverted or been licensed to UCLA/UCLB for future development or partnering.

On February 9, 2021, we issued and sold (i) 20,900,321 ordinary shares, nominal value £0.10 per share, at a purchase price of $6.22 per share (the "Purchase Price"), which was the closing sale price of our ADSs on the Nasdaq Global Select Market on February 4, 2021, and (ii) 3,215,434 non-voting ordinary shares, nominal value £0.10 per share, at the Purchase Price (together (i) and (ii), the "Private Placement"). The Private Placement resulted in net proceeds to us of $143.6 million after deducting placement agent fees of $6.0 million and other offering-related costs of $0.4 million. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement we entered into with the purchasers named therein on February 4, 2021. All non-voting ordinary shares issued and sold in the Private Placement have since been converted to ordinary shares. The ADSs representing the ordinary shares issued in the Private Placement were registered for resale on an automatic shelf registration statement on Form S-3 filed with the SEC on April 8, 2021.

Business update regarding COVID-19

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

In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy, have placed significant restrictions on travel. While some restrictions have been relaxed since the beginning of the pandemic, some restrictions are still in place. In the U.S. and UK, our office-based employees have been primarily working from home since March 2020. Limitations on travel and other social distancing measures may have an effect on our preclinical and clinical activities and regulatory timelines. While our clinical sites are still treating and following up with patients in clinical trials, these centers are also devoting significant resources to patients with COVID-19 and may need to devote additional resources as variants of COVID-19 lead to a potential rise in hospitalizations, which could limit their ability to enroll additional patients in ongoing clinical studies.

As additional variants of the virus proliferate, potential renewed 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 ongoing COVID-19 pandemic and response efforts may have an impact in the future on our or our third-party suppliers' and CDMO partners' ability to manufacture our products in development. Any prolonged material disruptions to our employees, suppliers, CDMOs, vendors or patients could impact our operating results and could lead to impairments. To date, we have recorded impairments on long-lived assets that are due to a combination of a corporate restructuring and COVID-19 market impacts. In addition, our ability to access the capital markets could be impacted if there are future disruptions to capital markets that result from the COVID-19 pandemic.

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

Components of our results of operations

Product revenue, net

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

Collaboration revenue

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

Cost of product sales

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

A portion of our inventory includes raw materials that were expensed prior to approval of Libmeldy, referred to as zero cost inventories. Cost of sales for newly launched products will not include the full cost of manufacturing until the initial pre-launch inventory is depleted, and additional inventory is purchased, manufactured and sold. Therefore, the cost of product sales reflects a portion but not all of the manufacturing costs of our products. We expect to continue to use zero cost raw materials through 2023.

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 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;
- research and development related costs associated with the Company's collaboration arrangement with Pharming;
- costs of outside consultants, including their fees, share-based compensation and related travel expenses;
- 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, costs related to our collaboration with Pharming, and other operating costs;
- upfront, milestone and management fees for maintaining licenses under our third-party licensing agreements; and
- grant awards or other government incentives unrelated to income taxes that we earn that are recorded as an offset to the related research and development costs incurred.

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

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and contract manufacturing organizations in connection with our preclinical and clinical development activities. License fees and other costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. License fees and other costs incurred

prior to designating a product candidate for development are included in unallocated costs. We do not allocate employee costs, costs associated with our early-stage discovery efforts, laboratory supplies, and facilities, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials or the manufacturing requirements to conduct those clinical trials. We expect that our research and development expenses will continue to decline due to the portfolio updates and workforce reduction we undertook in 2022 as well as the completion of certain activities to support an OTL-200 BLA submission.

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, commercial, corporate and business development, and administrative functions. Selling, general and administrative expenses also include professional fees for legal, patent, accounting, auditing, tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs. Selling, general and administrative expenses also include distributor-related fees related to product sales analogous to a commission in arrangements where the distributor is considered to be an agent.

Other income (expense), net

Interest income

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

Interest expense

Interest expense consists of interest associated with our Credit Facility with MidCap Financial, which we entered into in May 2019, and amended and restated in May 2021. The Amended Credit Facility bears a variable interest rate at a rate of 5.95% above LIBOR, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility. LIBOR phases out in June 2023, at which point the Company and MidCap will agree on a new reference rate.

Other income (expense)

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

Results of operations

Comparison of the three months ended June 30, 2022 and 2021

The following table summarizes our results of operations for the three months ended June 30, 2022 and 2021:

	Three Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Product revenue, net	$ 3,781	$ —	$ 3,781
Collaboration revenue	587	—	587
Total revenue	4,368	—	4,368
Costs and operating expenses			
Cost of product sales	1,122	—	1,122
Research and development	21,965	21,750	215
Selling, general and administrative	13,730	14,263	(533)
Total costs and operating expenses	36,817	36,013	804
Loss from operations	(32,449)	(36,013)	3,564
Other income (expense):			
Interest income	213	113	100
Interest expense	(672)	(593)	(79)
Other income (expense):	(18,227)	634	(18,861)
Total other income (expense), net	(18,686)	154	(18,840)
Loss before income taxes	(51,135)	(35,859)	(15,276)
Income tax (expense) benefit	219	(750)	969
Net loss	$ (50,916)	$ (36,609)	$ (14,307)

Revenue

Product revenue, net

During the three months ended June 30, 2022 and 2021, we recognized product revenue from sales of Libmeldy and Strimvelis in Europe as follows:

	Three Months Ended June 30,		
	2022	2021	Change
	(in thousands)		
Libmeldy	$ 3,145	$ —	$ 3,145
Strimvelis	636	—	636
	$ 3,781	$ —	$ 3,781

Libmeldy received approval from the European Commission in December 2020, and we made our first commercial sales of Libmeldy during the quarter ended March 31, 2022.

We announced in March 2022 that we would discontinue our investment in and seek alternatives for Strimvelis.

Collaboration revenue

During the three months ended June 30, 2022 and 2021, we recognized revenue of $0.6 million and nil, respectively, under our collaboration agreement with Pharming. We recognize revenue using the cost-to-cost input method. Under this method, revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred.

Cost of product sales

Cost of sales for the three months ended June 30, 2022 consisted of costs to manufacture, distribute and administer Libmeldy and Strimvelis and royalty payments due to third parties related to these sales. The gross margin on our product revenue, net for the three months ended June 30, 2022, was enhanced by our use of zero cost inventories. Utilizing the per unit average cost of materials that were purchased prior to approval and expensed that were utilized in the manufacturing process for our products sold during the period, cost of product sales for the three months ended June 30, 2022 would have been approximately $1.3 million.

Research and development expenses

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

	Three Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 6,789	$ 3,439	$ 3,350
Primary immune deficiencies	2,174	6,268	(4,094)
Blood disorders	502	165	337
Other research and preclinical programs under development	1,149	1,619	(470)
Total direct research and development expenses:	10,614	11,491	(877)
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	8,280	9,280	(1,000)
Share-based compensation	1,383	2,135	(752)
Restructuring costs	(494)	—	(494)
Amortization of Strimvelis loss provision	—	(368)	368
Research and development tax credit	(1,764)	(4,246)	2,482
Facility and other	3,946	3,458	488
Total indirect research and development expenses	11,351	10,259	1,092
Total research and development expenses	$ 21,965	$ 21,750	$ 215

Direct research and development expenses for neurometabolic programs increased by $3.4 million. Direct expenses associated with OTL-200 increased by $3.4 million compared to the three months ended June 30, 2021, primarily due to an increase in manufacturing and clinical development related costs. Direct research and development expenses for primary immune deficiency-related programs

decreased by $4.1 million for the three months ended June 30, 2022 compared to the three months ended June 30, 2021, due to the de-prioritization of these programs.

Unallocated research and development costs and offsets to research and development expenses increased by $1.1 million compared to the three months ended June 30, 2021. The increase was primarily due to a decrease of $2.5 million in our U.K. Research and Development Tax Credit, which is recorded as an offset to research and development expense, partially offset by decreased personnel related costs of $1.0 million, shared-based compensation of $0.8 million and restructuring costs of $0.5 million. Research and development tax credits decreased by $2.5 million due to a decrease in qualifying costs. Decreased personnel and share-based costs were primarily due to the impact of our strategic restructuring plan that we undertook in the quarter ended March 31, 2022. We also recorded an adjustment to our restructuring accrual in the quarter ended June 30, 2022 for changes to our plan.

Selling, general and administrative expenses

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

	Three Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 4,408	$ 5,033	$ (625)
Share-based compensation	2,362	3,406	(1,044)
Restructuring costs	23	—	23
Consulting, professional, and insurance-related costs	3,114	3,537	(423)
Marketing, promotions, and advocacy	1,540	1,049	491
Facilities and other costs	2,283	1,238	1,045
Total selling, general, and administrative expenses:	$ 13,730	$ 14,263	$ (533)

Selling, general and administrative expenses were $13.7 million in the three months ended June 30, 2022, compared to $14.3 million in the three months ended June 30, 2021, a decrease of $0.5 million. Personnel and share-based compensation decreased by an aggregate $1.7 million as a function of lower headcount primarily due to our strategic restructuring we undertook in the quarter ended March 31, 2022. These decreases were partially offset by increases in facilities and other costs of $1.0 million, primarily due to increased shareholder and ADS administration costs and an increase of $0.5 million in marketing, promotions, and advocacy. Marketing, promotions, and advocacy increased due primarily to an increase of $0.9 million in distributor-related fees related to product sales analogous to a commission in arrangements where the distributor is considered to be an agent, partially offset by a decrease of $0.7 million in market access fees, a component of marketing, promotions, and advocacy costs.

Other income (expense), net

Other income (expense), net for the three months ended June 30, 2022 and 2021 consisted of losses of $18.7 million and income of $0.2 million, respectively. During the three months ended June 30, 2022, we had net realized and unrealized losses on foreign currency transactions of $18.2 million, compared to net realized and unrealized gains of $0.6 million for the three months ended June 30, 2021. These unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar to Pounds sterling exchange rate. Additionally, we had interest income of $0.2 million in the three months ended June 30, 2022, compared to $0.1 million in the three months ended June 30, 2021 and interest expense of $0.7 million, compared to $0.6 million. The increase in interest expense of $0.1 million in the three months ended June 30, 2022 as compared to the three months ended June 30, 2021 is attributable to a higher outstanding principal balance.

Comparison of the six months ended June 30, 2022 and 2021

The following table summarizes our results of operations for the six months ended June 30, 2022 and 2021:

	Six Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Product revenue, net	$ 8,840	$ —	$ 8,840
Collaboration revenue	1,052	—	1,052
Total revenue	9,892	—	9,892
Costs and operating expenses			
Cost of product sales	2,693	—	2,693
Research and development	50,199	42,785	7,414
Selling, general and administrative	27,029	28,314	(1,285)
Total costs and operating expenses	79,921	71,099	8,822
Loss from operations	(70,029)	(71,099)	1,070
Other income (expense):			
Interest income	282	284	(2)
Interest expense	(1,347)	(1,131)	(216)
Other income (expense):	(24,279)	1,992	(26,271)
Total other income (expense), net	(25,344)	1,145	(26,489)
Loss before income taxes	(95,373)	(69,954)	(25,419)
Income tax (expense) benefit	161	(1,837)	1,998
Net loss	$ (95,212)	$ (71,791)	$ (23,421)

Revenue

Product revenue, net

During the six months ended June 30, 2022 and 2021, we recognized product revenue from sales of Libmeldy and Strimvelis in Europe as follows:

	Six Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Libmeldy	$ 8,204	$ —	$ 8,204
Strimvelis	636	—	636
	$ 8,840	$ —	$ 8,840

Libmeldy received approval from the European Commission in December 2020, and we made our first commercial sales of Libmeldy during the quarter ended March 31, 2022.

We announced in March 2022 that we would discontinue our investment in and seek alternatives for Strimvelis.

Collaboration revenue

During the six months ended June 30, 2022 and 2021, we recognized revenue of $1.1 million and nil, respectively, under our collaboration agreement with Pharming. We recognize revenue using the cost-to-cost input method. Under this method, revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred.

Cost of product sales

Cost of sales for the six months ended June 30, 2022 consisted of costs to manufacture, distribute and administer Libmeldy and Strimvelis and royalty payments due to third parties related to these sales. The gross margin on our product revenue, net for the six months ended June 30, 2022, was enhanced by our use of zero cost inventories. Utilizing the per unit average cost of materials that were purchased prior to approval and expensed that were utilized in the manufacturing process for our products sold during the period, cost of product sales for the six months ended June 30, 2022 would have been approximately $3.3 million.

Research and development expenses

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

	Six Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 13,847	$ 9,180	$ 4,667
Primary immune deficiencies	5,657	8,871	(3,214)
Blood disorders	3,005	292	2,713
Other research and preclinical programs under development	2,239	2,649	(410)
Total direct research and development expenses:	24,748	20,992	3,756
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	17,213	18,233	(1,020)
Share-based compensation	3,538	5,011	(1,473)
Restructuring costs	1,570	—	1,570
Amortization of Strimvelis loss provision	(276)	(814)	538
Research and development tax credit	(5,101)	(7,800)	2,699
Facility and other	8,507	7,163	1,344
Total indirect research and development expenses	25,451	21,793	3,658
Total research and development expenses	$ 50,199	$ 42,785	$ 7,414

Direct research and development expenses for neurometabolic programs increased by $4.7 million. Direct expenses associated with OTL-200 increased by $6.1 million compared to the six months ended June 30, 2021, primarily due to an increase manufacturing and clinical development related costs. Direct expenses for OTL-201 decreased by $0.7 million compared to the six months ended June 30, 2021, primarily due to decreases in manufacturing and clinical costs. Direct expenses for OTL-203 decreased by $0.8 million, primarily due to a decrease of $1.2 million in manufacturing costs, partially offset by an increase in clinical costs of $0.7 million.

Direct research and development expenses for primary immune deficiency-related programs decreased by $3.2 million compared to the six months ended June 30, 2021,due to de-prioritization of the primary immune deficiency-related programs.

Direct research and development expenses for blood disorder-related programs increased by $2.7 million in the six months ended June 30, 2022 compared to the six months ended June 30, 2021. The increase was primarily due to accruing of long-term follow up cost associated with returning the program to the licensee and other wind-down costs relating to the programs.

Unallocated research and development costs and offsets to research and development expenses increased by $3.7 million compared to the six months ended June 30, 2021 due primarily to a decrease in our research and development tax credits, which is recorded as an offset to research and development expense, and increases in restructuring costs and facility and other. Research and development tax credits decreased by $2.7 million due to a decrease in qualifying costs. We recorded $1.6 million of restructuring charges in the six months ended June 30, 2022, primarily related to employee terminations. Facility and other increased by $1.3 million due to a $1.8 million increase in platform development costs, partially offset by a $0.5 million decrease in facilities and professional service fees. These increases in research and developments costs were partially offset by decreases in personnel costs and share based compensation of $1.0 million and $1.5 million, respectively, as a result of our reduced headcount as part of our strategic restructuring.

Selling, general and administrative expenses

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

	Six Months Ended June 30,		
	2022	2021	Change
		(in thousands)	
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 9,037	$ 10,420	$ (1,383)
Share-based compensation	5,060	6,797	(1,737)
Restructuring costs	440	105	335
Consulting, professional, and insurance-related costs	6,578	6,490	88
Marketing, promotions, and advocacy	2,313	2,152	161
Facilities and other costs	3,601	2,350	1,251
Total selling, general, and administrative expenses:	$ 27,029	$ 28,314	$ (1,285)

Selling, general and administrative expenses were $27.0 million in the six months ended June 30, 2022, compared to $28.3 million in the six months ended June 30, 2021, a decrease of $1.3 million. Personnel and share-based compensation decreased by $3.1 million as a function of lower headcount during the first half of 2022, partially offset by $0.3 million of employee termination expenses incurred in connection with the strategic restructuring. Facilities and other costs increased by $1.3 million, primarily from increased shareholder and ADS administration costs.

Other (expense) income, net

Other (expense) income, net for the six months ended June 30, 2022 and 2021 consisted of losses of $25.3 million and income of $1.1 million, respectively. During the six months ended June 30, 2022, we had net realized and unrealized losses on foreign currency transactions of $24.3 million, compared to net realized and unrealized gains of $2.0 million for the six months ended June 30, 2021. These unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar to Pounds sterling exchange rate. Interest income was $0.3 million in each of the six months ended June 30, 2022 and 2021 and interest expense was $1.3 million and $1.1 million, respectively. The increase in interest expense of $0.2 million in the six months ended June 30, 2022 as compared to the six months ended June 30, 2021 is attributable to a higher outstanding principal balance.

Liquidity and capital resources

From our inception through June 30, 2022, we have not generated significant revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We acquired Strimvelis and the program that is now Libmeldy from GSK in April 2018, and our product candidates are in various phases of preclinical and clinical development. In December 2020, the European Commission granted standard marketing authorization for Libmeldy. We launched Libmeldy in Europe and generated product revenue during the three and six months ended June 30, 2022. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our IPO and follow-on offering, proceeds from the sale of ordinary shares in our private placement, proceeds from the sale of convertible preferred shares, proceeds associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program, reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., and our Original Credit Facility and our Amended Credit Facility.

On February 27, 2020 we entered into a Sales Agreement with Cowen and Company, LLC ("Cowen"), as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. On March 24, 2022, we delivered written notice to Cowen to terminate the Sales Agreement, effective as of March 30, 2022, pursuant to Section 11(b) thereof. Prior to termination, we had not sold any ADSs pursuant to the Sales Agreement. As a result of the termination of the Sales Agreement, we will not offer or sell any ADSs under the Sales Agreement.

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

Cash flows

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

	Six Months Ended June 30,	
	2022	2021
	(in thousands)	
Net cash used in operating activities	$ (45,975)	$ (75,294)
Net cash provided by (used in) investing activities	44,751	(34,191)
Net cash provided by financing activities	137	153,856
Effect of exchange rate changes on cash and cash equivalents	(1,355)	423
Net increase (decrease) in cash, cash equivalents, and restricted cash	$ (2,442)	$ 44,794

Operating activities

During the six months ended June 30, 2022, operating activities used $46.0 million of cash, primarily resulting from our net loss of $95.2 million, partially offset by net non-cash charges of $35.2 million and net cash provided by changes in our operating assets and

liabilities of $14.1 million. Cash provided by changes in our operating assets and liabilities consisted primarily of a decrease in our research and development tax credit receivable of $13.3 million, an increase in accounts payable, accrued expenses and other currently liabilities of $4.3 million and a decrease $0.8 million of prepaid expenses, other current assets and other assets, partially offset by a $3.0 million increase in accounts receivable and a net change in our right-of-use assets and lease liabilities of $1.1 million. Non-cash charges to operating activities of $35.2 million was primarily due to unrealized foreign currency and other non-cash adjustments of $25.1 million, which consisted of unrealized foreign currency transaction losses of $23.9 million on intercompany accounts by our UK subsidiary and deferred income taxes of $1.2 million. Non-cash charges to operating activities also included $8.6 million in share-based compensation expense and depreciation and amortization expense of $1.4 million.

During the six months ended June 30, 2021, operating activities used $75.3 million of cash, primarily resulting from our net loss of $71.8 million. Cash usage from changes in our operating assets and liabilities was $24.1 million, which was primarily driven by an increase in our U.K. research and development tax credit receivable of $7.8 million and payout of our annual bonuses of $7.2 million, offset by accruals associated with license intangible assets of $2.6 million. Non-cash adjustments to operating activities of $20.6 million was primarily due to $11.8 million in non-cash share-based compensation expense, offset by $0.8 million in amortization of the Strimvelis loss provision as an offset to research and development expense. Further, there were other non-cash adjustments of $7.7 million, including unrealized foreign currency transaction gains on intercompany accounts by our U.K. subsidiary, using $6.3 million that were driven by foreign currency revaluation, and deferred income taxes of $1.4 million.

Investing activities

During the six months ended June 30, 2022, net cash provided by investing activities was $44.8 million, due to proceeds from sales and maturities of marketable securities of $97.2 million, partially offset by purchases of marketable securities of $50.9 million and purchases of property and equipment of $1.6 million.

During the six months ended June 30, 2021, net cash used in investing activities was $34.2 million, due to purchases of marketable securities of $167.0 million and purchases of property and equipment of $0.9 million, partially offset by proceeds from sales and maturities of marketable securities of $133.5 million.

Financing activities

During the six months ended June 30, 2022, net cash provided by financing activities was $0.1 million, consisting of proceeds from employee equity plans.

During the six months ended June 30, 2021, net cash provided by financing activities was $153.9 million consisting of proceeds of $143.6 million from the issuance of ordinary shares in our private placement, net of offering costs, proceeds of $7.4 million from the modification of our debt facility, net of debt issuance costs paid and proceeds from employee equity plans of $2.8 million.

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 Libmeldy in Europe, and for any product candidates for which we may submit for and obtain marketing approval anywhere in the world;
- continue our development of our product candidates, including continuing our ongoing advanced registrational trials and supporting studies, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- perform research and development activities with respect to potential new product candidates;
- conduct investigational new drug application, or IND, and or clinical trial application, or CTA,-enabling studies for our 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, cash equivalents, and marketable securities will enable us to fund our operating expenses, capital expenditures and debt service payments into 2024. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

Critical Accounting Policies and Estimates

Our condensed consolidated financial statements are prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of our financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that of our critical accounting policies which are described under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations—Critical Accounting Policies and Significant Judgments and Estimates" in our Annual Report, the following accounting policies involve the most judgment and complexity:

- United Kingdom research and development tax credit
- Accrued research and development expenses
- Valuation of share-based compensation
- Product revenue, net

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. Other than the below new critical accounting policy related to product revenue, net, there have been no material changes to our critical accounting policies since December 31, 2021.

Product revenue, net

Libmeldy

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

We recognize revenue when control of promised goods is transferred to a customer at an amount that reflects the consideration to which we expect to be entitled in exchange for those goods. Control of the product transfers upon infusion of the product. To determine revenue recognition, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfied the performance obligations. We only apply the five-step model to contracts when collectability of the consideration to which we are entitled in exchange for the goods we transfer to the customer is determined to be probable. In certain regions of Europe and the Middle East, we utilize distributors to act in an agent capacity including for patient identification and other related functions. We are exclusively responsible for product fulfillment and retain inventory risk and pricing discretion of the product. Evaluation of these key indicators support our assertion that we maintain control over the product prior to delivery to the patient. We have concluded that we are the principal in these transactions and we record the associated revenue on a gross basis.

Amounts are recorded as accounts receivable when the right to the consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. We expense incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that would have been recognized is one year or less or the amount is immaterial. As of June 30, 2022, we have not capitalized any costs to obtain contracts.

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

These reserves are based on estimates of the amounts earned or to be claimed on the related sales and are classified as a liability. Our estimates of reserves established for variable consideration are calculated based upon an application of the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts. These estimates reflect our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data, and current expectations around final pricing. The amount of variable consideration that is included in the transaction price may be subject to constraint and is included in net product revenue only to the extent that it is probable that a significant reversal in the amount of the

cumulative revenue recognized will not occur in a future period. Actual amounts of consideration received may ultimately differ from our estimates. If actual results vary, we adjust these estimates, which could have an effect on earnings in the period of adjustment. The following is a summary of the types of variable consideration the Company records:

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

Trade discounts and allowances: We may offer customers discounts, such as prompt pay discounts to remit payment in accordance with the stated terms of the invoice and fees for distribution services. These discounts are explicitly stated in the contracts and recorded in the period the related product revenue is recognized. Our payment terms can range from 30 days to under 1 year. We estimate which customers will earn these discounts and fees and deducts these discounts and fees in full from gross product revenue and accounts receivable at the time we recognize the related revenue.

Product returns: Based on the timing of revenue recognition upon treatment with the patient, we do not expect any returns of our products.

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

Item 3. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate sensitivity

As of June 30, 2022, we had cash, cash equivalents, marketable securities, and restricted cash of $175.2 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying UK and US bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

We have borrowed $33.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 5.95% plus LIBOR. As of June 30, 2022, the carrying value of the term loans under the credit facility was $27.5 million.

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.

Foreign currency exchange risk

The Company is exposed to foreign currency exchange risk because it currently operates in the United Kingdom and the United States. The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the ultimate parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises finance and expends cash in U.S. dollars, and expects to continue to do so in the future. Exchange gains or losses arising from foreign currency transactions are included in the determination of net loss for the respective periods. We recorded net realized and unrealized foreign currency losses of $18.2 million for the three months ended June 30, 2022 and net realized and unrealized foreign currency gains of $0.6 million for the three months ended June 30, 2021. We recorded net realized and unrealized foreign currency losses of $24.3 million for the six months ended June 30, 2022 and net realized and unrealized foreign currency gains of $2.0 million for the six months ended June 30, 2021. These foreign currency transaction gains and losses are primarily related to revaluation of intercompany balances that are denominated in U.S. dollar that are recorded on entities whose functional currency is not the U.S. Dollar. The losses are included in other income (expense), net in our condensed consolidated statements of operations and comprehensive loss.

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

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

Item 4. Controls and Procedures.

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

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this report. In designing and evaluating our disclosure controls and procedures, our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial officer have concluded based upon the evaluation described above that, as of June 30, 2022, our disclosure controls and procedures were effective at the reasonable assurance level.

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

Changes in Internal Control Over Financial Reporting

During the three months ended June 30, 2022, there have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) or 15d-15(d) under the Exchange Act) that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

PART II—OTHER INFORMATION

Item 1. Legal Proceedings.

From time to time, we may be a party to litigation or subject to claims incident to the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, we currently believe that the final outcome of these ordinary course matters will not have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. As of June 30, 2022, 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 prospects. This Quarterly Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in forward-looking statements as a result of certain factors including the risks described below and elsewhere in this Quarterly Report and our other SEC filings. See "Special Note Regarding Forward-Looking Statements" above.

Risks related to our financial position and need for additional capital

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

Since inception, we have incurred net losses. We incurred net losses of $95.2 million and $71.8 million for the six months ended June 30, 2022 and 2021, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares and through sales of our ADSs in our initial public offering and follow-on offering. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Libmeldy in the European Union, building a global commercial infrastructure to support commercialization of Libmeldy (OTL-200) and our product candidates if such product candidates are approved, as well as refining our team. Prior to the approval of Libmeldy in Europe in December 2020, Strimvelis was our only product approved for sale, and in March 2022, we announced our decision to discontinue our investment in and seek alternatives for Strimvelis. Absent the realization of sufficient revenue from product sales of Libmeldy, and from sales of our current or future product candidates, if approved, we may never attain profitability.

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

- seek marketing approvals for our product candidates that successfully complete clinical trials or meet primary endpoints, if any;
- market and sell Libmeldy in Europe and grow our commercial infrastructure for the commercialization (or anticipated commercialization) of any product candidates that we may submit for and obtain marketing approval anywhere in the world;
- continue the development of our product candidates;
- continue our ongoing clinical trials and any required regulatory updates for certain deprioritized programs;
- conduct investigational new drug application, or IND, or clinical trial application, or CTA, enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates or future product candidates, including new research programs in genetic subsets of frontotemporal dementia, or FTD, and Crohn's disease;
- seek to identify and develop, acquire or in-license additional product candidates or technologies;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates, to support technology and process innovation, and to support manufacturing of product to commercial scale;
- establish partnerships with contract development and manufacturing organizations, or CDMOs;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility in the long-term;

- hire and retain 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, or experience high levels of absenteeism due to the COVID-19 pandemic;
- develop, maintain, expand and protect our intellectual property portfolio; and
- comply with our obligations as a public company.

Since receiving marketing authorization, only a limited number of patients have been treated with Strimvelis and Libmeldy. There is no assurance that revenue from sales of Libmeldy alone will be sufficient for us to become profitable. To become and remain profitable, we must develop and eventually commercialize product candidates with greater market potential. This will require us to be successful in a range of challenging activities, and our expenses will increase as we seek to complete necessary preclinical studies and clinical trials of our product candidates, and manufacture, market and sell Libmeldy or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenue that is significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

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

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

- completing research and 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;
- successfully commercializing Libmeldy in Europe and other product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related post-marketing commitments for regulatory compliance for Libmeldy and Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Libmeldy and Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Libmeldy and Strimvelis, if sales are resumed, and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Libmeldy and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and manufacturing capabilities;

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

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

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

Our operations have consumed a substantial amount of cash since our inception, and we recorded negative cash flows from operating activities during the first half of 2022, primarily due to our net loss of $95.2 million for that period. We expect to continue to incur substantial expenses in connection with our ongoing activities, which may increase over time, particularly as we (i) continue to commercialize Libmeldy in Europe, (ii) continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and (iii) continue to enhance and optimize our vector technology and manufacturing processes. In addition, we expect to incur significant expenses related to product sales, post-marketing regulatory commitments, medical affairs, marketing, manufacturing, distribution and quality systems to support Libmeldy and any other products for which we obtain marketing approval. Furthermore, we will continue to incur costs associated with operating as a public company, including with respect to the system and process evaluations and testing of our internal controls and financial reporting. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on reasonable terms, or at all, we would be forced to delay, reduce or eliminate certain of our ongoing activities, such as research and development programs and commercialization efforts.

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

- the success of our commercialization efforts and market acceptance of Libmeldy in Europe;
- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities to support Libmeldy in Europe and any other products for which we obtain marketing approval, including costs relating to quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors on a timely basis for Libmeldy and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related post-marketing commitments for regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our product candidates or future product candidates, including the need to conduct long-term follow-up for up to 15 years for our development programs and additional clinical trials to support marketing approvals for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs, including our ability to resolve delays in trial enrollment as a result of the COVID-19 pandemic;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Libmeldy and 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 Libmeldy and Strimvelis. In addition, Libmeldy and any other products for which we obtain and maintain marketing approval may not achieve commercial success. Any product revenue from our product candidates, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

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

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

We were incorporated in August 2018 to become a holding company for Orchard Therapeutics (Europe) Limited, which was founded in 2015, and its subsidiaries. Our operations to date have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring certain of our product candidate portfolios and rights to our technology, identifying potential product candidates, undertaking 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 commercialization of Libmeldy. We have not yet demonstrated the ability to manufacture products on a commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they might be if we had a longer operating history. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and setbacks.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. Russia's invasion of Ukraine has led to, and may continue to cause, volatility in the capital markets. Volatility among foreign currencies could impact our results of operations. As an example, we had net realized and unrealized losses on foreign currency transactions of $24.3 million during the six months ended June 30, 2022, compared to net realized and unrealized gains of $2.0 million during the six months ended June 30, 2021. Unrealized gains and losses are driven primarily by intercompany balances denominated in currencies other than our functional currency, the U.S. Dollar.

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

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

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

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

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

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

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

For example, although the FDA cleared our IND application for OTL-200 in 2020 and we received Regenerative Medicine Advanced Therapy, or RMAT, designation in 2021, there can be no guarantee we will be successful in resolving open matters to the FDA's satisfaction before the intended BLA submission, in which case the adequacy of our clinical endpoints, natural history analysis and CMC data package to support a potential BLA submission and approval will be review issues. We continue to engage with the FDA as we seek to address its recommendations and identify expeditious paths to market for our product candidates.

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

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

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

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

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

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. The FDA has established the Office of 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 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 might be materially and adversely affected.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In certain conditions, such as MLD and ADA-SCID, the potency of a product candidate may be directly measured through enzymatic activity; however, for an intracellular protein such as WAS, developing an assay is more complex. Based on written feedback from the FDA, we believe that development of a functional potency assay for OTL-103 for WAS may require additional time and further investment. If an adequate potency assay for a product candidate is not available, if we face delays (including delays related to the COVID-19 pandemic), or if the FDA or EMA require additional tests or recommend a different approach to support the potency of any of our product candidates, regulatory approval for any such product candidates will be delayed and such regulators might request additional clinical data to support comparability analysis. Similarly, if one or more of these regulatory authorities does not accept that our drug product manufactured with HSCs derived from the patient's mobilized peripheral blood is comparable to drug product manufactured with HSCs derived from the patient's bone marrow, any regulatory approval would be limited to drug product manufactured with HSCs derived from the patient's bone marrow until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials. In April 2020, the FDA advised us that we may need to generate additional data to demonstrate the comparability of our OTL-200 drug product derived from the patient's mobilized peripheral blood and the OTL-200 drug product derived from the patient's bone marrow, and that the data provided to date are inadequate to determine if the two materials are comparable. Further, the FDA requested that we provide data that demonstrates the comparability of the different OTL-200 product formulations used across our trials. Failure to demonstrate such comparability, or if we are required to conduct additional testing or additional clinical trials, potentially at additional sites, would delay any marketing authorization and adversely affect the commercial viability of our product candidates and may adversely affect our ability to generate revenue, as a result of which our business, prospects, financial condition and results of operations may suffer.

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

As part of our strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates. We may spend several years completing our development of any particular current or future product candidates, and failure can occur at any stage. Even if we receive approval of a product candidate, we may not achieve commercial success for a variety of factors, including failure to achieve market acceptance in the medical community and the availability of third-party insurance coverage or reimbursement. For example, we received standard marketing authorization for Libmeldy in December 2020 from the European Commission and launched the commercialization of Libmeldy in Europe in early 2022, but there is no assurance that our commercialization efforts will be successful or that our pricing assumptions or our assumptions about the size of the anticipated patient population will prove to be accurate.

The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. For example, in May 2020, we announced our decision to reduce investment in the development of OTL-101 for ADA-SCID (for which we subsequently terminated our license) and OTL-300 for TDT to focus on other product candidates in our pipeline and new research and development efforts in less rare diseases. Additionally, in March 2022 we announced our decision to focus on severe neurometabolic diseases and early research programs, and to discontinue our investment in and seek strategic alternatives for our programs in rare primary immune deficiencies, including OTL-103 for treatment of WAS, OTL-102 for treatment of X-CGD and Strimvelis. Our focus on the advancement of our other product candidates may ultimately prove to be unsuccessful or less successful than if we had continued to prioritize such deprioritized product candidates, and if we choose to reprioritize such deprioritized product candidates in the future, we may experience delays that would not have otherwise occurred, due to inefficiencies from loss of organizational knowledge and ramp up costs. Moreover, we may be unable to realize the savings we expect to achieve by deprioritizing certain programs, which could result from, among other things, higher than expected transition or termination costs.

Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

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

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

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

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

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

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

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

For example, although sustained clinical activity has been observed in clinical trials to date for Libmeldy (OTL-200), follow-up in these clinical trials is ongoing and there can be no assurance that the results, in each case as of the applicable primary endpoint measurement date, seen in clinical trials of any of our product candidates ultimately will result in success in clinical trials or provide adequate support for marketing approvals by the FDA, in the case of Libmeldy, without conducting further clinical trials. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical trials, and may not be repeated or observed in ongoing or future trials involving our product candidates. There are limited data concerning long-term safety and efficacy following treatment with our product candidates. Our product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in 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 generally, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. Additionally, the ongoing COVID-19 global pandemic has had and may continue to have a sustained impact on our ability to recruit and follow-up with patients either due to continued or renewed restrictions on travel or shelter-in-place orders or policies or due to changes in patient willingness to participate in trials or travel to study sites in the wake of the pandemic. Additionally, COVID-19 related study site policies may create delays or setbacks in our ability to continue to enroll or to dose patients. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

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

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

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

- difficulty in establishing or managing relationships with academic partners or contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;

- the absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

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

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

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and the outcome is uncertain. 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 creates challenges for patient follow-up visits for all programs. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

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

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

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

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

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

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

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

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

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

As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to maintain this pace and delays or setbacks are possible in the future, including where a pre-approval inspection or an inspection of clinical sites is required and, due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspection during the review period. In 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may similarly experience delays in their regulatory activities due to the COVID-19 pandemic.

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

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

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

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

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

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

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

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by the EMA or other regulatory authorities in other countries or jurisdictions, and approval by the EMA or another regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. For example, though we received standard marketing authorization of Libmeldy (OTL-200) from the European Commission in December 2020, there is no guarantee that we will receive approval from the FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional 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 may be harmed.

Additionally, in June 2016, the UK held a referendum in which a majority of voters approved an exit from the EU, or Brexit, and the UK formally left the EU on January 31, 2020. There was a transition period during which EU pharmaceutical laws continued to apply to the UK, which expired on December 31, 2020. However, the EU and the UK have concluded a Trade and Cooperation Agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore currently aligns in the most part with EU regulations, however it is possible that these regimes will diverge in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. For example, the new Clinical Trials Regulation, which became effective in the EU on January 31, 2022, and provides for a streamlined clinical trial application and assessment procedure covering multiple EU Member States, has not been implemented into UK law, and a separate application will need to be submitted for clinical trial authorization in the UK. The separate, and potentially diverging, regulatory regimes between Great Britain and the EU may increase our regulatory burden of applying for and obtaining authorization in Great Britain and the EU.

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

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

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

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

The FDA and comparable other regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. OTL-200 for MLD and OTL-103 for WAS received RMAT designation from the FDA, and OTL-203 for MPS-IH received a Priority Medicines, or PRIME, designation from EMA. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

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

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

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

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

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

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

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

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

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan 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 EU. 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 such products would generate sufficient return in the EU to justify the necessary investment their development. In either case, the applicant for orphan designation must also demonstrate that no satisfactory method of diagnosis, prevention, or treatment for the condition has been authorized for marketing in the EU (or, if a method exists, the new product would be a significant benefit to those affected by the condition).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. This includes compliance with cGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third-party manufacturers would be required to ensure that all of our processes, quality systems, methods, and equipment are compliant with cGMP. Failure by us or by any of our third-party partners, including suppliers, manufacturers, and distributors to comply with EU laws and the related national laws of individual EU Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after 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, EU legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that EMA and the competent authorities of the EU Member States have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct a burdensome collection of data regarding the risks and benefits of marketed products and may be required to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical trials, which may be time-consuming and expensive and could impact our profitability. Non-compliance with such obligations can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

Risks related to manufacturing and supply

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

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

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

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

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

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

Since March 2020, when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Ongoing travel restrictions and other uncertainties continue to impact oversight operations both domestic and abroad and it is unclear when standard operational levels will resume. The FDA is continuing to complete mission-critical work, prioritize other higher-tiered inspectional needs (e.g., for-cause inspections), and carry out surveillance inspections using risk-based approaches for evaluating public health. Should FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the ongoing COVID-19 pandemic and may experience delays in their regulatory activities.

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

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

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

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

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

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

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

We may be delayed or unable to identify, engage, successfully coordinate or qualify with treatment centers in the regions we are targeting as part of our commercial 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 or drug products or inventory loss may harm our operating results and financial condition.

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

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

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

Risks related to our reliance on third parties

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

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

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

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

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

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

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

If our collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under such collaborations. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. 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 product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing shareholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation

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

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

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

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

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

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

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

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

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

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our preclinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing preclinical and clinical programs. 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 EEA, and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. The FDA, EMA or comparable foreign regulatory authorities may deem the clinical data generated in our clinical trials unreliable and may require us to perform additional clinical trials before approving our marketing applications if, among other things, we fail to exercise adequate oversight over any of our academic partners or CROs or if our academic partners or CROs do not successfully carry out their respective contractual duties or obligations, fail to meet expected deadlines or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements. We cannot assure that upon a regulatory inspection of us, our academic partners or our CROs or other third parties performing services in connection with our clinical trials, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under applicable cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

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

Additionally, the FDA or EMA may disagree with the sufficiency of our right of reference to the 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 or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

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

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

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

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

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

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

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

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;

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

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

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

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

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

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

Risks related to commercialization of our product candidates

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

We are working to successfully commercialize Libmeldy in Europe, and we intend to commercialize our product candidates, if approved, in the United States, Europe and other markets. Given the relative rarity of the indications that we are targeting, we are commercializing Libmeldy, and we currently intend to commercialize any product candidates that are approved, directly with specialized teams. We currently have a limited marketing and sales team, and we must build and expand our commercial infrastructure

and capabilities or make arrangements with third parties to perform those services. If we are unable to do so, we may be unable to generate sufficient revenue to sustain our business.

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

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

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

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

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

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

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

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

We rely primarily on know-how and trade secret protection for aspects of our proprietary technologies, Libmeldy, Strimvelis and our product candidates. We do not have any issued patents covering Libmeldy, Strimvelis or our product candidates. This means that barriers to entry that typically apply in the case of pharmaceutical and biopharmaceutical companies with issued patents covering aspects of their proprietary technologies, products and product candidates, such as composition of matter claims, will generally not apply to our commercial products or our product candidates, and this may expose us to competition from other biopharmaceutical companies, particularly those companies that possess greater financial resources and more mature product candidate development, manufacturing, marketing and distribution resources than we do. Although our product candidates, if approved, may be eligible for marketing and data exclusivities in, for example, the United States and Europe, these exclusivities would not prevent another

biopharmaceutical company from conducting its own clinical trials to develop and seek regulatory approval of a competitive product. We are not the only company that is developing and commercializing products using a lentiviral-based autologous *ex vivo* gene therapy approach, and these competitive approaches may be comparable or superior to our approach. One or more of these companies may seek to develop products that compete directly with our commercial products or one or more of our product candidates, the result of which could have a material adverse effect on our business. In addition, many universities and private and public research institutes are active in our target disease areas.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks related to the impact of COVID-19

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

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

In response to the pandemic, we implemented a work from home policy. Most of our administrative employees continue to work outside of our offices, and we have reduced on-site staff significantly. 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 or renewed 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. Our clinical sites have devoted significant resources to patients with COVID-19, which could limit their ability to enroll additional patients in ongoing clinical trials or follow-up with existing patients. Some factors from the COVID-19 pandemic that have delayed and may continue to delay or otherwise adversely affect enrollment in or the progress of our clinical trials for some or all of our product candidates, as well as our business generally, include:

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

Trial procedures (particularly any procedures that may be deemed non-essential), patient dosing, shipment of our product candidates, distribution of clinical trial materials, study monitoring, site inspections and data analysis may be paused or delayed due to the above factors or other reasons related to the pandemic. Furthermore, if the coronavirus, including new variants of the virus, continues to spread, or recurs in the future, or if approved vaccines are not as effective as anticipated or are significantly delayed in being administered, some patients and clinical investigators may not be able to comply with clinical trial protocols or we may see

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

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

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

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

Risks related to our business operations

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

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

stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

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

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

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

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

We have acquired rights to several programs and we may in the future acquire rights to additional programs. If we are unable to effectively manage these programs, our future results may suffer.

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

Furthermore, in some instances, we may decide to discontinue our investment in acquired programs after we've invested time and capital into such programs. For example, in May 2020, we announced a reduction of the investment in and scope of our OTL-101 and OTL-300 programs and, based on the reallocation of capital, we determined to prioritize other programs, including research and development projects in less rare indications. Additionally, in March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis, OTL-103 for treatment of WAS and OTL-102 for treatment of X-CGD. We may be unable to realize the savings we expect to achieve by deprioritizing certain programs, which could result from, among other things, higher than expected transition or termination costs.

Our failure to adequately address the financial, operational or legal risks of acquisitions, license arrangements or other strategic transactions related to our current or future product candidates could harm our business. Financial aspects of such future transactions that could alter our financial position, or operating results include:

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

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

- challenges associated with managing an increasingly diversified business;
- disruption of our ongoing business;

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

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

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

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

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

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

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

or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

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

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

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

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

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

Recruiting and retaining 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 March 2022, we announced (i) that we would discontinue our investment in and seek alternatives for Strimvelis, OTL-103 for treatment of WAS and OTL-102 for treatment of X-CGD and (ii) a reduction of our workforce of approximately 30%. The workforce reduction may negatively impact our clinical, regulatory, technical operations and commercial functions, which could have a negative impact on our ability to successfully develop, and ultimately, commercialize our product candidates. 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. Our future financial performance and our ability to develop our product candidates or additional assets will depend, in part, on our ability to effectively manage any future growth or restructuring, as the case may be.

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

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

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

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

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

In June 2021, the U.S. Supreme Court, or Supreme Court, dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an Executive Order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The Executive Order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

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

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

It is unclear how other healthcare reform measures of the Biden administrations or other efforts, if any, to challenge repeal or replace the ACA, will impact our business.

Other legislative changes potentially affecting our business have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2030 unless additional Congressional action is taken. Pursuant to the CARES Act and subsequent legislation, however, these reductions were suspended from May 2020 through March 31, 2022 due to the COVID-19 pandemic. Then, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022.

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.

In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain health care facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B drug pricing program, and CMS subsequently altered the FYs 2019 and 2018 reimbursement formula on specified covered outpatient drugs, or SCODs. The court ruled this change was not an "adjustment" which was within the Secretary's discretion to make but was instead a fundamental change in the reimbursement calculation. However, most recently, on July 31, 2020, the U.S. Court of Appeals for the District of Columbia Circuit overturned the district court's decision and found that the changes were within the Secretary's authority. On September 14, 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), but was denied on October 16, 2020. Plaintiffs-appellees filed a petition for a writ of certiorari at the Supreme Court on February 10, 2021. On Friday July 2, 2021, the Supreme Court granted the petition. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any.

There have been several other actions taken at a federal level seeking to lower drug prices. At a federal level, President Biden signed an Executive Order in July 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the U.S. federal government pays for drugs, and address price gouging in the industry. The Executive Order also directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. The FDA released such implementing regulations in September 2020, which went into effect in November 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, in November 2020, CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021 and ending December 31, 2027. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada may materially and adversely affect the

price we receive for any of our product candidates. Additionally, in December 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors have been delayed until January 1, 2026. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that it will continue to seek new legislative measures to control drug costs.

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

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

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

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

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

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

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

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

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

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

- The federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties.
- The federal civil and criminal false claims laws and civil monetary penalty laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery.
- The anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program.
- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

- The U.S. federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.
- The federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs.
- The federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- Many states in the United States have enacted laws that regulate the privacy and security of certain types of personal information. For example, in California the California Consumer Protection Act (CCPA), which went into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. After a delay, the CCPA became subject to enforcement as of July 1, 2020. Although clinical trial data and protected health information subject to HIPAA are currently exempt from CCPA, we may be subject to the CCPA with respect to other personal information regarding California residents. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.
- Additionally, a new California ballot initiative, the California Privacy Rights Act, or "CPRA," was passed in November 2020. Effective starting on January 1, 2023, the CPRA imposes additional obligations on companies covered by the legislation and will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. The effects of the CCPA and the CPRA are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement or litigation.
- Certain other state laws impose similar privacy obligations, and we also expect anticipate that more states to may enact legislation similar to the CCPA, which provides consumers with new privacy rights and increases the privacy and security obligations of entities handling certain personal information of such consumers. The CCPA has prompted a number of proposals for new federal and state-level privacy legislation. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs or changes in business practices and policies.

Following the UK's withdrawal from the EU on January 31, 2020 and the end of the transitional arrangements agreed between the UK and EU, as of January 1, 2021, the GDPR was incorporated into UK domestic law. UK-based organizations doing business in the EU will need to continue to comply with the GDPR. The UK is now regarded as a third country under the EU GDPR, but the European Commission has issued a decision recognizing the UK as providing adequate protection under the EU GDPR. Therefore, transfers of personal data originating in the EU to the UK remain unrestricted. The UK Government has also confirmed that transfers of personal data originating in the UK to the EU may continue to flow freely.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute and False Claims Act and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the GDPR, 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 additional clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer or other processing of personal data regarding individuals in the EEA or the UK, including personal health data, is subject to the GDPR. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, where required obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, where required providing notification of data breaches, and taking certain measures when engaging third-party processors, including concluding data processing agreements, where required appointing data protection officers, where required conducting data protection impact assessments, and record-keeping. The GDPR also imposes strict rules and restrictions on the transfer of personal data to countries outside the EEA or the UK, including the United States (see below), and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20.0 million (£17.5 million) or 4% of annual global revenue, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. The GDPR may increase our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities.

Significantly, adequate safeguards must be implemented to enable the transfer of personal data outside of the EEA or the UK, in particular to the United States, in compliance with European and UK data protection laws. In June 2021, the European Commission issued new forms of standard contractual clauses for data transfers from controllers or processors in the EU/EEA (or otherwise subject to the EU GDPR) to controllers or processors established outside the EU/EEA (and not subject to the EU GDPR). The new standard contractual clauses replace the standard contractual clauses that were adopted previously under the Data Protection Directive. The UK is not subject to the European Commission's new standard contractual clauses but has published its own version of standard clauses, referred to as International Data Transfer Agreement, which was laid before Parliament in February 2022, and, entered into force in March 2022 to enable transfers originating from the UK. We will be required to implement these new safeguards when conducting restricted data transfers under the GDPR and doing so will require significant effort and cost.

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

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

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

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

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

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

- economic weakness, including inflation, or political instability in the United Kingdom and other non-U.S. economies and markets, 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 and the war in Ukraine;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the eligible members of the UK electorate for the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws or practice;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;

- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, fires and public health epidemics and pandemics, including the current COVID-19 global pandemic.

Risks related to our intellectual property

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

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

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

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

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

We are aware of third-party issued patents and patent applications relating to the lentiviral vectors used in the manufacture or use of one or more our product candidates or relating to one or more of our product candidates. If these patent rights were enforced against us, we believe that we have defenses against any such action, including that these patents would not be infringed by our product candidates or that these patents are not valid. However, if these patents were enforced against us and defenses to such

enforcement were unsuccessful, unless we obtain a license to these patents, which may not be available on commercially reasonable terms, or at all, we could be liable for damages and precluded from commercializing any products and product candidates that were ultimately held to infringe these patents, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

We are highly dependent on the intellectual property and data licensed to us by third parties that are important or necessary to the development of our technology and products and product candidates, including technology related to the manufacture and use of our products and product candidates. In particular, we do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis, Libmeldy or any of our lead product candidates. We have in-licensed certain know-how and data from GSK and Telethon-OSR, relating to Strimvelis, OTL-103 for WAS, Libmeldy, and OTL-300 for TDT, certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-IH, and certain other intellectual property for our clinical and preclinical programs. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

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

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

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the particular licensor may have the right to terminate such agreements. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may

impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected products and product candidates. Termination of our license agreements or reduction or elimination of our rights under them may result in our having to negotiate a new or reinstated agreement, which may not be available to us on equally favorable terms, or at all, which may mean we are unable to develop or commercialize the affected product or product candidate or cause us to lose our rights under the agreement. Any of the foregoing could have a material adverse effect on our business.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We may become involved in lawsuits to protect or enforce our patents, if issued, 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 future patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition.

Even if we establish infringement, misappropriation or another violation of our intellectual property rights, a court may decide not to grant an injunction against the offender and instead award only monetary damages, which may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public

announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our ADSs. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Any of the foregoing may have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

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

Changes in patent law in the United States and other jurisdictions could diminish the value of patents in general, 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. The Supreme Court issued a decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, or *Prometheus*, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as "administering" or "determining" steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. Thereafter, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the

claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. Subsequently, the Supreme Court issued its decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, or *Myriad*, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. *Myriad* held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent-eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible. Thereafter, the USPTO issued a guidance memorandum instructing USPTO examiners on the ramifications of the *Prometheus* and *Myriad* rulings and apply the *Myriad* ruling to natural products and principles including all naturally occurring nucleic acids.

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

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

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

Risks related to ownership of our securities

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

The trading price of our ADSs has fluctuated and 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 our current or future collaborators to successfully develop and commercialize product candidates for which we are eligible to receive milestone and royalty payments;
- failure by us to adequately scale our manufacturing capabilities and commercial and sales organization to succeed in our commercialization efforts of Libmeldy;
- failure by us to succeed in our ongoing commercialization of Strimvelis;
- failure by us to gain broad insurance coverage and reimbursement for our product candidates, if approved;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;

- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial or other projections we may provide to the public;
- failure by us to meet or exceed the financial or other projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- general economic, geopolitical and market conditions, including the significant disruptions to the U.S. and global economies and the related significant volatility and negative pressure in financial markets caused by the COVID-19 global pandemic, supply chain issues, inflationary pressures and the ongoing conflict in the Ukraine;
- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

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

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

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

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

Based upon our ordinary shares outstanding as of June 30, 2022, 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, and the approval of certain significant corporate transactions. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that our shareholders may believe are in their best interest as shareholders. Some of these persons or entities may have interests that are different than those of our other shareholders. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs were sold in our initial public offering and have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

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

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

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

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

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

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

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

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

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

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

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under

the federal securities laws has not been finally adjudicated by the Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs.

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

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

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

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

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

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

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

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

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

Sales of a substantial number of our ADS in the public market, or the perception that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. As of May 9, 2022, we had outstanding 125,905,065 voting shares. The holders of 8,611,375 shares of our ordinary shares are entitled to rights with respect to the registration of their ordinary shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these ordinary shares under the Securities Act would result in the ADSs representing them becoming freely tradable without restriction, except for ADSs purchased by affiliates. In addition, our directors, executive officers and other affiliates may establish, and certain executive officers, directors and affiliates have established, programmatic selling plans under Rule 10b5-1 of the Exchange Act, for the purpose of effecting sales of our ADSs. Generally, sales under such plans by our executive officers and directors require public filings. Any sales of securities by these shareholders, or the perception that those sales may occur, under such programmed selling plans, could have a material adverse effect on the trading price of our ADSs. In addition, as of March 31, 2022, 16,727,785 ordinary shares reserved for issuance upon the exercise of existing options outstanding and issuance of performance-based and time-based restricted shares under our current equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

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

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

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

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

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

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

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

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

The principal differences include the following:

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

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

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

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

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

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

We are not currently in compliance with the minimum bid price rule of the Nasdaq Global Select Market, and a delisting could limit the liquidity of our ADSs, increase their volatility and hinder our ability to raise capital.

In April 2022, we received a letter from the Nasdaq Stock Market ("Nasdaq") stating that we were not in compliance with the minimum bid price requirement for continued listing on the Nasdaq Global Select Market because the closing bid price for our ADSs was below $1.00 per share for 30 consecutive business days. The notice from Nasdaq has no immediate effect on the listing of our ADSs, and the ADSs will continue to be listed on the Nasdaq Global Select Market under the symbol "ORTX". We have been afforded a 180-calendar day period, or until October 3, 2022, to regain compliance with the minimum bid price requirement. The continued listing standard will be met if the closing bid price of our ADSs is at least $1.00 per share for a minimum of ten consecutive business days during the 180-calendar day period. If we are not in compliance by October 3, 2022, the Company may be afforded a second 180-calendar day period to regain compliance if it meets certain requirements. We intend to monitor the closing bid price of our ADSs and we are currently evaluating our options for regaining compliance, which could include adjusting the ADS-to-ordinary share ratio.

Delisting from the Nasdaq Global Select Market could make trading our ADSs more difficult for investors, potentially leading to declines in the trading price of our ADSs and decreased liquidity. We cannot ensure that our ADSs, if delisted from the Nasdaq Global Select Market, will be listed on another national securities exchange or quoted on an over-the-counter system. Other consequences of delisting could include an adverse effect on our ability to obtain equity financing on acceptable terms or at all, an increase in volatility of our ADS trading price, and a loss of confidence by shareholders, employees and business partners.

Risks related to taxation

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

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

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

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

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

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

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

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

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

We believe that we were not a CFC in the 2021 taxable year, but we may become a CFC in a subsequent taxable year. If we are classified as both a CFC and a passive foreign investment company, or PFIC (as discussed below), we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

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

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

We do not believe that we were a PFIC in the 2021 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. If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF election. A U.S. holder would also be able to make a mark-to-market election with respect to our ordinary shares or ADSs as long as those shares or ADSs constitute marketable securities under the Code.

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

As a UK incorporated and tax resident entity, we are subject to UK corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any UK corporation tax. As of December 31, 2021, we had cumulative carryforward tax losses of $506.2 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to UK profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus, broadly, an incremental 50% of UK taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a company that carries out extensive research and development activities, we seek to benefit from two UK research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure Credit program, or RDEC Program. Where available, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are 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. The U.K. Finance Act of 2021 introduced a cap on payable credit claims under the SME Program in excess of £20,000 with effect from April 2021 by reference to, broadly, three times the total PAYE and NICs liability of the company, subject to an exception which prevents the cap from applying. That exception requires the company to be creating, taking steps to create or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties, which does not exceed 15% of the total claimed. If such exception does not apply, this could restrict the amount of payable credit that we claim.

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

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

Under Section 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership by certain stockholders over a three-year period, the corporation's ability to use its pre-change tax attributes (such as research and development tax credits) to offset its post-change tax liabilities may be limited. We have completed several financings since our inception, which we believe have

resulted in an ownership change as defined by Section 382 of the Code. We may also experience ownership changes in the future as a result of subsequent shifts in our share ownership. As a result, if we incur U.S. federal tax liability, our ability to use our pre-change tax attributes to offset U.S. federal tax liability may be subject to limitations, which could potentially result in increased future tax liability to us.

Risks related to our Domicile

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

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

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

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

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether 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.

General Risk Factors

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

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

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

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

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

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

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

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

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

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

National and international regulators and law enforcement agencies have conducted investigations into a number of rates or indices known as "reference rates." Actions by such regulators and law enforcement agencies may result in changes to the manner in which certain reference rates are determined, their discontinuance, or the establishment of alternative reference rates. In particular, in July 2017, the Chief Executive of the UK Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA will no longer persuade or compel banks to submit rates for the calculation of LIBOR after 2021. This deadline was extended until June 2023 for a number of key U.S. dollar benchmark maturities.

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

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

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

We could be subject to securities class action litigation.

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

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

Not applicable.

Item 3. Defaults Upon Senior Securities.

Not applicable.

Item 4. Mine Safety Disclosures.

Not applicable.

Item 5. Other Information.

Not applicable.

Item 6. Exhibits.

Exhibit Number	Description
10.1	Lease Agreement, dated April 5, 2022, among 245 Hammersmith Road Nominee 1 Limited, 245 Hammersmith Road Nominee 2 Limited, 245 Hammersmith Road Limited Partnership, and Orchard Therapeutics (Europe) Limited.
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 (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101)

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

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

SIGNATURES

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

ORCHARD THERAPEUTICS PLC

Date: August 4, 2022

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: August 4, 2022

By: /s/ Frank E. Thomas

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

LEASE

Relating to premises known as Part 3rd Floor

245 Hammersmith Road, London W6 8PW

Dated: 5 April 2022

(1) 245 HAMMERSMITH ROAD NOMINEE 1 LIMITED, 245 HAMMERSMITH ROAD NOMINEE 2 LIMITED and 245 HAMMERSMITH ROAD LIMITED PARTNERSHIP (acting through its general partner 245 HAMMERSMITH ROAD GENERAL PARTNER LIMITED)

(2) ORCHARD THERAPEUTICS (EUROPE) LIMITED

CONTENTS

LAND REGISTRY PRESCRIBED CLAUSES

LR1. Date of lease	5 April 2022
LR2. Title number(s)	
LR2.1 Landlord's title number(s)	NGL692974.
LR2.2 Other title numbers	BGL125442, BGL125421, BGL125422, BGL125423 and BGL49405.
LR3. Parties to this lease	
Landlord	together: (1) **245 HAMMERSMITH ROAD NOMINEE 1 LIMITED** (incorporated and registered in England and Wales under company registration number 10259825) whose registered office is at One Coleman Street, London EC2R 5AA; (2) **245 HAMMERSMITH ROAD NOMINEE 2 LIMITED** (incorporated and registered in England and Wales under company registration number 10259717) whose registered office is at One Coleman Street, London EC2R 5AA; and (3) **245 HAMMERSMITH ROAD LIMITED PARTNERSHIP** (incorporated and registered in England and Wales under company registration number LP17488) whose principal place of business is at One Coleman Street, London, EC2R 5AA (acting by its general partner 245 HAMMERSMITH ROAD GENERAL PARTNER LIMITED (incorporated and registered in England and Wales under company registration number 10250842) whose registered office is at One Coleman Street, London, EC2R 5AA).
Tenant	**ORCHARD THERAPEUTICS (EUROPE) LIMITED** (incorporated and registered in England and Wales under company registration number 9759506) whose registered office is at 108 Cannon Street, London, EC4N 6EU.
LR4. Property	**In the case of a conflict between this clause and the remainder of this lease then, for the purposes of registration, this clause shall prevail.**
	The property described as the "Premises" in **clause 1** of this Lease subject to **clause 6.2.1** of this Lease.
LR5. Prescribed statements etc.	None.
LR6. Term for which the Property is leased	The term as specified in **clause 3.1** of this Lease.
LR7. Premium	None.

LR8. Prohibitions or restrictions on disposing of this lease	This Lease contains a provision that prohibits or restricts dispositions.
LR9. Rights of acquisition etc.	
LR9.1 Tenant's contractual rights to renew this lease, to acquire the reversion or another lease of the Property, or to acquire an interest in other land	None.
LR9.2 Tenant's covenant to (or offer to) surrender this lease	None.
LR9.3 Landlord's contractual rights to acquire this lease	None.
LR10. Restrictive covenants given in this lease by the Landlord in respect of land other than the Property	None.
LR11. Easements	
LR11.1 Easements granted by this lease for the benefit of the Property	As specified in this Lease at **Part 1 of Schedule 1**.
LR11.2 Easements granted or reserved by this lease over the Property for the benefit of other property	As specified in this Lease at **Part 2 of Schedule 1**.
LR12. Estate rentcharge burdening the Property	None.
LR13. Application for standard form of restriction	None.
LR14. Declaration of trust where there is more than one person comprising the Tenant	Not applicable.

LEASE

PARTIES

(1) the Landlord named in clause LR3 and any other person who becomes the immediate landlord of the Tenant (the "**Landlord**"); and

(2) the Tenant named in clause LR3 and its successors in title (the "**Tenant**").

IT IS AGREED AS FOLLOWS:

1. **DEFINITIONS** TC "1 DEFINITIONS" \l 1

This Lease uses the following definitions:

"1925 Act"

Law of Property Act 1925;

"1954 Act"

Landlord and Tenant Act 1954;

"1986 Act"

Insolvency Act 1986;

"1994 Act"

Law of Property (Miscellaneous Provisions) Act 1994;

"1995 Act"

Landlord and Tenant (Covenants) Act 1995;

"1996 Act"

Arbitration Act 1996;

"Act"

any act of Parliament and any delegated law made under it;

"AGA"

an authorised guarantee agreement (as defined in section 16 of the 1995 Act);

"Ancillary Rent Commencement Date"

the Term Start Date;

"Break Date"

20 February 2027 (being the day immediately preceding the fifth anniversary of the Term Start Date);

"**BREEAM**"

the BRE Environmental Assessment Method;

"Building"

the building known as 245 Hammersmith Road, London W6 8PW including all alterations, additions and improvements and all landlord's fixtures forming part of it at any time during the Term;

"Building Management Systems"

all or any of the following (that do not exclusively serve any Lettable Unit) used within or serving (i) the Building and/or (ii) the Podium:

(a) lighting systems;

(b) security, CCTV and alarm systems;

(c) access control systems;

(d) audio and audio-visual systems;

(e) wireless, phone, data transmission and other telecommunications systems;

(f) air ventilation and filtration;

(g) air-conditioning, heating and climate control systems;

(h) water heating, filtering and chilling systems; and

(i) fire detection, alarm and sprinkler systems;

and all control systems, plant, machinery, equipment, Supplies and Conducting Media used in connection with them;

"Business Day"

any day other than a Saturday, Sunday or a bank or public holiday in England and Wales and "**Business Days**" shall be interpreted accordingly;

"Car Park"

the car park within the Building and which is shown edged blue on Plan 5;

"Common Parts"

subject to **paragraph 4 of Part 2 of Schedule 1**, any part of, or anything in, the Building that does not form part of a Lettable Unit and that is used or available for use by:

(a) the Tenant in common with others (including the communal roof terrace on the 10th floor of the Building designated by the Landlord for the use of the tenants of the Building);

(b) the Landlord in connection with the provision of the Services; or

(c) visitors to the Building;

"Conducting Media"

any media for the transmission of Supplies but not including any service risers or any other airspace through which the media run;

"Current Guarantor"

someone who, immediately before a proposed assignment, is either a guarantor of the Tenant's obligations under this Lease or a guarantor of the obligations given by a former tenant of this Lease under an AGA;

"Electronic Communications Apparatus"

"electronic communications apparatus" as defined in section 151 of the Communications Act 2003;

"End Date"

the last day of the Term (however it arises);

"Environmental Performance"

all or any of the following:

(a) the consumption of energy and associated generation of greenhouse gas emissions;

(b) the consumption of water;

(c) waste generation and management; and

(d) any other environmental impact arising from the use or operation of the Premises or the Building;

"EPB Regulations"

the Energy Performance of Buildings (England and Wales) Regulations 2012;

"EPC"

an Energy Performance Certificate and Recommendation Report (as defined in the EPB Regulations);

"External Works"

subject to **clause 4.11.5**, all or any of the following works outside the Premises:

(a) connecting to existing Conducting Media under **paragraph 1 of Part 1 of Schedule 1**;

(b) the installation of any apparatus permitted under the exception to **clause 4.11.1(d)**;

(c) the installation of any Plant and Conducting Media between them and the Premises under **paragraph 5 of Part 1 of Schedule 1**;

"Group Company"

in relation to any company, any other company within the same group of companies as that company within the meaning of section 42 of the 1954 Act;

"Hazardous Material"

any substance, whether in solid, liquid or gaseous form, which is capable of causing harm to human health or to the environment whether on its own or in combination with any other substance;

"Insurance Rent"

the sums described in **paragraph 1.1 of Schedule 4**;

"Insured Risks"

the risks of fire (including subterranean fire), lightning, explosion, storm, flood, subsidence, landslip, heave, earthquake, burst or overflowing water pipes, tanks or apparatus, impact by aircraft or other aerial devices and any articles dropped from them, impact by vehicles, terrorism, riot, civil commotion and malicious damage to the extent, in each case, that cover is generally available on normal commercial terms in the UK insurance market at the time the insurance is taken out, and any other risks against which the Landlord reasonably insures from time to time, subject in all cases to any excesses, limitations and exclusions imposed by the insurers;

"Interest Rate"

three per cent above the base rate for the time being in force of National Westminster Bank PLC (or any other UK clearing bank specified by the Landlord in writing);

"Lease"

this lease, which is a "new tenancy" for the purposes of section 1 of the 1995 Act, and any document supplemental to it;

"Lettable Unit"

accommodation within the Building from time to time let or occupied or intended for letting or occupation, but excluding accommodation let or occupied for the purposes of providing any of the Services;

"Main Rent"

the rent payable under **clause 3.2**;

"Notice"

any notice, notification or request given or made under this Lease;

"Outgoings"

all or any of:

(a) all existing and future rates, taxes, duties, charges, and financial impositions charged on the Premises and/or any Plant or any owner or occupier of them except for:

(i) tax (other than VAT) on the Rents payable; and

(ii) any tax arising from the Landlord's (or landlord of the Podium Leases) dealing with its own interests;

(b) Supply Costs for the Premises and/or any Plant; and

(c) a fair and reasonable proportion of the Outgoings referred to in **paragraphs (a) and (b)** charged in respect of:

(i) the Podium; and

(ii) any other parts of the Building other than the Premises and/or any Plant

to the extent that those amounts do not form part of the Service Costs;

"Parking Space Rent"

the sum of three thousand five hundred pounds (£3,500) per annum;

"Permitted Hours"

24 hours a day 365 days per year;

"Permitted Use"

the use of the Premises as offices and laboratory space within Class E of the Schedule to the Town and Country Planning (Use Classes) Order 1987 (as enacted at the date of this Lease);

"Permitted Works"

any works or installations (including Tenant's Business Alterations and any External Works) to which the Landlord has consented or for which, under **clause 4.10**, the Landlord's consent is not required;

"Planning Acts"

every Act for the time being in force relating to the use, development, design, control and occupation of land and buildings;

"Planning Permission"

any permission, consent or approval given under the Planning Acts;

"Plans"

any of the plans as numbered contained in this Lease;

"Plant"

plant and other equipment erected pursuant to the Tenant's rights in **paragraph 5 of Part 1 of Schedule 1**;

"Plant Area"

the following areas:

(a) the area on Floor 10 and which is shown edged red on Plan 3; and

(b) the area on Floor 12 and which is shown edged red on Plan 4

or any other area substituted for it under **paragraph 5.2** of **Part 1 of Schedule 1**;

"Podium"

that land comprised within the registered titles listed in LR2.1 and LR2.2 (but excluding that land comprising the Building) and which is shown (for identification purposes only) on Plan 2 comprising:

(a) the area (at podium level together with the staircase up to the podium) shaded green;

(b) the ground floor piazza shaded light blue; and

(c) the staircase shaded orange;

"Podium Leases"

the following leases:

(a) lease of land adjacent to 1 Butterwick, Hammersmith dated 23 June 2016 made between (1) Aviva Life & Pensions UK Limited and (2) Legal And General Assurance (Pensions Management) Limited (and which is registered under title number BGL125421);

(b) lease of land outside of Metro Building, 1 Butterwick, Hammersmith dated 23 June 2016 made between (1) Rockspring Transeuropean VI Hammersmith Metro (Jersey) Limited and (2) Legal And General Assurance (Pensions Management) Limited (and which is registered under title number BGL125422); and

(c) lease of land outside of the hotel at 1 Shortlands, Hammersmith dated 23 June 2016 made between (1) Accor UK Pensions & Leisure Hotels Limited and (2) Legal And General Assurance (Pensions Management) Limited (and which is registered under title number BGL125423);

"Premises"

the premises known as part of the 3rd floor offices forming part of the Building and shown edged red on Plan 1:

(a) including:

(i) all plaster and other internal surfacing materials and finishes on the structural walls, floors and ceilings of the Premises and on the other structural parts of the Building within or bounding the Premises;

(ii) windows and window frames but excluding the external decorative finishes of any windows on the external walls of the Building;

(iii) doors and door frames;

(iv) the plaster and other internal surfacing and finishes on any non-structural walls separating the Premises from any Common Parts;

(v) one half severed vertically of any non-structural walls separating the Premises from any adjoining Lettable Units;

(vi) the entirety of any non-structural walls wholly within the Premises;

(vii) all Conducting Media and landlord's plant, equipment and fixtures exclusively serving the Premises including the Tenant's fire detection, alarm and sprinkler systems (if any) up to the point of connection with the Landlord's fire detection, alarm and sprinkler systems;

(viii) all tenant's fixtures; and

(ix) any Permitted Works (other than any External Works) carried out; but

(b) excluding:

(i) all load bearing and exterior walls and the floors and ceilings of the Premises (other than those included above);

(ii) all structural parts of the Building;

(iii) the glass walls, windows, frames and structure of any exterior curtain walling;

(iv) the entirety (subject to paragraph (a)(iv) of this definition) of any non-structural walls separating the Premises from any Common Parts;

(v) the airspace within any service risers that run through the Premises;

(vi) the Landlord's fire detection, alarm and sprinkler systems (if any) up to the point of connection with the Tenant's fire detection, alarm and sprinkler systems; and

(vii) the Building Management Systems (if any) within the Premises;

"Rent Commencement Date"

29 June 2023 (subject to **paragraph 3.3** of **Schedule 4**);

"Rent Days"

25th March, 24th June, 29th September and 25th December;

"Rent Review Date"

21 February 2027;

"Rents"

the Main Rent, the Insurance Rent, the Service Charge, the Parking Space Rent, any VAT payable on them and any interest payable under **clause 4.5**;

"Risk Period"

the period that the Landlord in its absolute discretion decides, being a minimum of four years, starting on the date of the relevant damage or destruction;

"Service Charge"

subject to the provisions of **paragraph 6 of Part 1 of Schedule 3**, a fair proportion (calculated on a floor area basis or any other method as the Landlord decides from time to time and notifies to the Tenant) of the Service Costs;

"Service Charge Exclusions"

the costs listed in **Part 4 of Schedule 3**;

"Service Costs"

the aggregate costs (including VAT that is not recoverable by the Landlord from HM Revenue & Customs) incurred by the Landlord in providing the Services and paying the costs listed in **Part 3 of Schedule 3** after excluding any Service Charge Exclusions;

"Services"

the services provided by the Landlord listed in **Part 3 of Schedule 3**;

"Supplies"

water, gas, air, foul and surface water drainage, electricity, oil, telephone, heating, cooling, energy, telecommunications, internet, data communications and similar supplies or utilities;

"Supply Costs"

the costs of Supplies including procurement costs, meter rents and standing charges and any taxes or levies payable on them;

"Tenant's Business Alterations"

so long as they do not affect the structural integrity of the Building, any of the following in relation to the Premises or the structural or non-structural walls or the ceiling and floor slabs bounding the Premises that are not within any other Lettable Unit:

(a) the creation of openings in the walls, ceiling and floor slabs within or bounding the Premises for the passage of the Tenant's Conducting Media; and

(b) fixing holes drilled into the floor or ceiling slabs, blockwork or plaster;

"Term"

the period of this Lease;

"Term End Date"

20 February 2032;

"Term Start Date"

21 February 2022;

"Uninsured Risk"

the risk of damage to or destruction of the Premises by any of the Insured Risks to the extent that it:

(a) is not insured against because, at the time the insurance is taken out or renewed, insurance is not generally available in the UK market on normal commercial terms; or

(b) is not, at the date of the damage or destruction, insured against by reason of a limitation or exclusion imposed by the insurers

but will not include loss or damage (or the risk of it) caused by reason of the Tenant's act or failure to act;

"VAT"

value added tax or any similar tax from time to time replacing it or performing a similar function;

"VAT Supply"

a "supply" for the purpose of the Value Added Tax Act 1994; and

"Wireless Data Services"

the provision of wireless data, voice or video connectivity or wireless services permitting or offering access to the internet or any wireless network, mobile network or telecommunications system that involves a wireless or mobile device.

2. **INTERPRETATION** TC "2 INTERPRETATION" \l 1

In this Lease:

2.1 "notify", "notifies" or "notifying" means notify, notifies or notifying in writing in accordance with **clause 6.3**;

2.2 where appropriate, the singular includes the plural and vice versa, and one gender includes any other;

2.3 all headings are for ease of reference only and will not affect the construction or interpretation of this Lease;

2.4 obligations owed by or to more than one person are owed by or to them jointly and severally;

2.5 an obligation to do something includes an obligation not to waive any obligation of another person to do it;

2.6 an obligation not to do something includes an obligation not to permit or allow another person to do it;

2.7 the Tenant will be liable for any breaches of its obligations in this Lease committed by:

2.7.1 any authorised occupier of the Premises or its or their respective employees, licensees or contractors; or

2.7.2 any person under the control of the Tenant or acting under the express or implied authority of the Tenant;

2.8 reference to either the Landlord or the Tenant having a right of approval or consent under this Lease means a prior written approval or consent, which must not be unreasonably withheld or delayed except where this Lease specifies that either the Landlord or the Tenant has absolute discretion;

2.9 where the Landlord has the right to impose regulations or to approve, decide, designate, nominate, request, require, specify, stipulate or express an opinion on any matter or thing under this Lease,

that right will be subject to a condition that the Landlord will act reasonably and properly when exercising that right except where this Lease specifies that the Landlord has absolute discretion;

2.10 references to the provision of plans, drawings, specifications or other documents means their provision in hard copy, electronically in PDF format or in any other easily readable format as may be appropriate having regard to the purpose for which they are provided and the nature of the information that they contain, but not in a format that is proprietary to a particular computer system or program that cannot be imported into or easily read by another computer system or program;

2.11 references to a Schedule are to a Schedule to this Lease and the Landlord and the Tenant must comply with their respective obligations in them;

2.12 apart from in **clause 4.6.1**, where either the Tenant or the Landlord must pay any costs that the other incurs (or any proportion of them), those costs must be reasonable and proper and reasonably and properly incurred;

2.13 references to any sums being payable on demand or when demanded mean being payable when demanded in writing;

2.14 the Landlord's rights under **clause** 4.10 and **Part 2 of Schedule 1** may also be exercised by:

2.14.1 (to the extent referred to in the Podium Leases) the landlord of the Podium Leases;

2.14.2 those authorised by the Landlord; and

2.14.3 (to the extent referred to in the Podium Leases) by those authorised by the landlord of the Podium Leases;

2.15 reference to "the Podium", "the Building", "the Common Parts" or "the Premises" means the whole or an individual part or parts unless inappropriate in the context used;

2.16 reference to "adjoining premises" means any land or buildings adjoining or nearby the Building, whether or not owned by the Landlord (unless express reference is made to the Landlord's ownership of those premises);

2.17 references to an Act are to that Act as amended from time to time and to any Act that replaces it but references to the Town and Country Planning (Use Classes) Order 1987 are to that Order as in force at the date of this Lease;

2.18 "includes", "including" and similar words are used without limitation or qualification to the subject matter of the relevant provision;

2.19 if any provision is held to be illegal, invalid or unenforceable, the legality, validity and enforceability of the remainder of this Lease will be unaffected;

2.20 if a person must take a matter into consideration that person must have reasonable regard to it but the final decision remains at that person's absolute discretion; and

2.21 references to a clause or schedule are references to a clause or schedule of this Lease and references in a schedule to a paragraph are references to paragraphs in that schedule.

3. **DEMISE, TERM AND RENT** TC "3 DEMISE, TERM AND RENT" \l 1

3.1 The Landlord leases the Premises to the Tenant with full title guarantee subject to the variations set out in **clause 6.10**:

3.1.1 for a term starting on the Term Start Date and ending on the Term End Date;

3.1.2 together with the rights listed in **Part 1 of Schedule 1**;

3.1.3 excepting and reserving to the Landlord the rights listed in **Part 2 of Schedule 1**;

3.1.4 subject to the matters contained or referred to in title numbers NGL692974, BGL125442, BGL125421, BGL125422, BGL125423 and BGL49405;

3.1.5 subject to any easements, rights and privileges currently existing and affecting the Premises; and

3.1.6 subject to any rights reserved by the Podium Leases so far as they affect the Premises (including any rights on the part of any of the landlords under the Podium Leases to terminate any of the Podium Leases).

3.2 The Tenant must pay as rent:

3.2.1 for the period starting on the Rent Commencement Date and ending on 28 December 2024 four hundred and seventy thousand two hundred and eighty six pounds (£470,286) yearly;

3.2.2 for the period of starting on 29 of December 2024 and ending on the day before the Rent Review Date nine hundred and forty thousand five hundred and seventy two pounds (£940,572) yearly; and

3.2.3 during the remainder of the Term, the rent set out in **clause 3.2.1** as increased (if at all) under **Schedule 2**.

3.3 Main Rent is not payable for any period before the Rent Commencement Date.

3.4 If the Tenant does not serve any notice under **clause 8.1** then, subject to **paragraph 3.3** of **Schedule 4**, for the period of 20 months commencing on the Rent Review Date, the Tenant shall only be obliged to pay (in the manner referred to in **clause 3.7**) 50% of the Main Rent applicable for such period. Thereafter, and for the remainder of the Term, the Tenant shall be obliged to pay 100% of the Main Rent.

3.5 Starting on the Ancillary Rent Commencement Date the Tenant must pay as rent:

3.5.1 Service Charge due under **clause 4.3** and **Schedule 3**; and

3.5.2 Insurance Rent; and

3.5.3 Parking Space Rent.

3.6 The Tenant must pay as rent VAT under **clause 4.4**.

3.7 The Main Rent is payable by equal quarterly payments in advance on the Rent Days in every year. The first payment will be for the period starting on (and to be paid on) the Rent Commencement Date and ending on the last day of that quarter.

3.8 The Parking Space Rent is payable by equal quarterly payments in advance on the Rent Days in every year. The first payment will be for the period starting on (and to be paid on) the Ancillary Rent Commencement Date and ending on the last day of that quarter.

3.9 The Rents and all other sums payable under this Lease must be paid by the Tenant by standing order to the United Kingdom bank account notified by the Landlord in writing to the Tenant.

3.10 The Tenant must not make any legal or equitable deduction, set-off or counterclaim from any payment due under this Lease unless required to do so by law.

4. **TENANT'S OBLIGATIONS** TC "4 TENANT'S OBLIGATIONS" \l 1

4.1 **Main Rent** TC "4.1 Main Rent" \l 2

The Tenant must pay the Main Rent when due.

4.2 **Outgoings** TC "4.2 Outgoings" \l 2

4.2.1 The Tenant must pay all Outgoings (with the exception of those referred to in **clause 4.2.2**) when demanded.

4.2.2 If the Landlord loses the benefit of any rates relief or exemption after the End Date because the Tenant has received that benefit before the End Date, the Tenant must pay the Landlord on demand an amount equal to the relief or exemption that the Landlord has lost.

4.2.3 If so required by the Landlord, the following provisions will apply in respect of the Supply Costs for the Premises and/or Plant:

(a) the accounting period will be the period ending on 30 June in each year (or otherwise as the Landlord may decide and notify to the Tenant) or the End Date if sooner;

(b) until the Supply Costs for the Premises for each accounting period have been calculated, the Tenant must pay, by equal quarterly payments on the Rent Days, a provisional sum by way of Supply Costs for the Premises at the level that the Landlord requires;

(c) the Tenant must also pay on demand any sum or sums that the Landlord requires where the sums held on account by the Landlord in respect of the Supply Costs for the Premises are insufficient to meet the actual Supply Costs for the Premises;

(d) when the Supply Costs for the Premises for each accounting period have been calculated:

(i) the Tenant must pay on demand any amount by which the actual Supply Costs in respect of the Premises for the relevant accounting period exceed the on-account payments received; and

(ii) the Landlord must credit the amount by which the on-account payments received exceed the actual Supply Costs in respect of the Premises for the relevant accounting period against the next payment or payments to be made by the Tenant under this clause 4.2.2. Any amount owing at the End Date must be repaid to the Tenant within one month of its calculation; and

(e) the End Date will not affect the Tenant's obligation to pay or the Landlord's right to recover Supply Costs for the Premises after the End Date where this has not been calculated and demanded before the End Date.

4.3 **Service Charge** TC "4.3 Service Charge" \l 2

The Tenant must pay the Service Charge in accordance with **Part 1 of Schedule 3**.

4.4 **VAT** TC "4.4 VAT" \l 2

4.4.1 The Tenant must pay:

(a) VAT on any consideration in respect of a VAT Supply to the Tenant by the Landlord at the same time as the consideration is paid and on provision of a valid VAT invoice addressed to the Tenant; and

(b) on demand VAT (and interest, penalties and costs where these are incurred because of anything the Tenant does or fails to do) charged in respect of any VAT Supply to the Landlord in respect of the Premises where that VAT is not recoverable by the Landlord from HM Revenue & Customs.

4.4.2 The Tenant must not do anything that would result in the disapplication of the option to tax in respect of the Landlord's interest in the Building.

4.5 **Interest on overdue payments** TC "4.5 Interest on overdue payments" \l 2

The Tenant must pay interest on the Rents and on all other sums not paid on or by the due date (or, if no date is specified, not paid within 10 Business Days after the date of demand). Interest will be payable at the Interest Rate for the period starting on the due date (or date of demand) and ending on the date of payment.

4.6 **Reimburse costs incurred by the Landlord** TC "4.6 Reimburse costs incurred by the Landlord" \l 2

The Tenant must pay on demand the Landlord's costs (including legal and surveyor's charges and bailiff's and enforcement agent's fees) and disbursements in connection with:

4.6.1 any breach of the Tenant's obligations in this Lease, including the preparation and service of a notice under section 146 of the 1925 Act, whether or not forfeiture is avoided by an order of the court;

4.6.2 any application by the Tenant for consent under this Lease, whether that application is withdrawn or consent is granted or lawfully refused, except in cases where the Landlord is required to act reasonably and the Landlord unreasonably refuses to give consent;

4.6.3 the preparation and service of any notice by the Landlord under section 17 of the 1995 Act or section 81 Tribunals, Courts and Enforcement Act 2007; and

4.6.4 the preparation and service of a schedule of dilapidations served no later than three months after the End Date.

4.7 **Third party indemnity** TC "4.7 Third party indemnity" \l 2

4.7.1 The Tenant must indemnify the Landlord against all actions, claims, demands made by a third party, all costs, damages, expenses, charges and taxes payable to a third party and the Landlord's own liabilities, costs and expenses incurred in defending or settling any action, claim or demand in respect of any personal injury or death, damage to any property and any infringement of any right arising from:

(a) the state and condition of the Premises or the Tenant's use of them;

(b) the exercise of the Tenant's rights; or

(c) the carrying out of any Permitted Works.

4.7.2 In respect of any claim covered by the indemnity in **clause 4.7.1**, the Landlord must:

(a) give notice to the Tenant of the claim as soon as reasonably practicable after receiving notice of it;

(b) provide the Tenant with any information and assistance in relation to the claim that the Tenant may reasonably require, subject to the Tenant paying to the Landlord all costs incurred by the Landlord in providing that information or assistance; and

(c) mitigate its loss (at the Tenant's cost) where it is reasonable for the Landlord to do so.

4.8 **Insurance** TC "4.8 Insurance" \l 2

The Tenant must comply with its obligations in **Schedule 4**.

4.9 **Repair and decoration** TC "4.9 Repair and decoration" \l 2

4.9.1 The Tenant must:

(a) keep the Premises and any External Works and/or any Tenant's Business Alterations in good and substantial repair and condition and clean and tidy;

(b) keep all Conducting Media, plant, equipment or fixtures forming part of the Premises and any External Works properly maintained and in good working order in accordance with good industry practice, the requirements of any Acts and any requirements of the Landlord's insurers (subject to the Tenant being provided with details of such insurer's requirements on request); and

(c) replace (where beyond reasonable economic repair) any Conducting Media and plant, equipment or fixtures forming part of the Premises and any External Works with items of equivalent or better quality.

4.9.2 The Tenant must promptly replace any damaged glass forming part of the Premises with glass of equivalent appearance and of the same or better quality.

4.9.3 The Tenant must clean and repair all floor coverings in the Premises as often as reasonably necessary and, in the final three months of the Term, renew and replace them with floor coverings of a colour and quality first approved by the Landlord.

4.9.4 The Tenant must decorate the Premises as and when necessary and in the final six months of the Term. The colour scheme for the final internal redecoration must first be approved by the Landlord.

4.9.5 The obligations under this **clause 4.9** apart from **clause 4.9.2** exclude:

(a) damage by any Insured Risk, except to the extent that payment of any insurance money is refused because of anything the Tenant does or fails to do and the Tenant has not complied with **paragraph 1.1.3 of Schedule 4**; and

(b) damage by any Uninsured Risk.

4.10 **Allow entry** TC "4.10 Allow entry" \l 2

4.10.1 The Tenant must allow the Landlord to enter and inspect the Premises.

4.10.2 If the Landlord requires the Tenant to remedy any breach of the Tenant's obligations regarding the state and condition of the Premises or to remove any unauthorised alterations then the Tenant must comply with those requirements immediately in the case of an emergency or, in all other cases, begin to comply with those requirements within one month after being notified of them and diligently complete any works required.

4.10.3 If the Tenant does not comply with **clause 4.10.2**, the Landlord may enter the Premises and carry out any works required itself. The Tenant must repay, as a debt on demand, all the costs the Landlord incurs in so doing. The Landlord's rights under **clause 6.1** will be unaffected.

4.11 **Alterations** TC "4.11 Alterations" \l 2

4.11.1 The Tenant must not:

(a) build any new structure on, or alter the external appearance of, the Podium or cut into the Podium or make any alterations or additions to the Podium.

(b) build any new structure on, or alter the external appearance of, the Premises or cut into any structural part of the Building, except for Tenant's Business Alterations;

(c) do or omit to do anything which adversely affects the efficiency of the use of energy (including the efficiency of the air-conditioning serving the Premises) or water, the Environmental Performance or sustainability characteristics of the Premises or the Building, including the EPC and BREEAM ratings;

(d) make any alterations to the Premises which would make the existing EPC rating for the Premises or the Building prior to such alterations being carried out worse;

(e) make any alterations to the Premises which would require a new EPC to be obtained unless the Tenant has demonstrated to the reasonable satisfaction of the Landlord that such new EPC will show an asset rating that is not less than the EPC rating existing for the Premises or the Building prior to such alterations being carried out; or

(f) install Electronic Communications Apparatus or apparatus relating to Wireless Data Services within the Premises, except where intended only to serve the lawful

occupier's business at the Premises and the installation of such Electronic Communications Apparatus or Apparatus relating to Wireless Data Services must be subject to Landlord's prior consent.

4.11.2 Landlord's consent is not required for the installation or removal of tenant's fixtures or for the installation and removal of, or alterations to internal demountable partitioning that will not have an adverse impact on the Environmental Performance of the Premises, the Building or the Building Management Systems, but the Tenant must notify the Landlord promptly after completing those works and provide the Landlord with "as built" drawings within 28 days after completion of those works.

4.11.3 The Tenant must not, without the Landlord's consent:

(a) do any other works to the Premises;

(b) carry out or install any External Works;

(c) make any Tenant's Business Alterations; or

(d) install any apparatus permitted under the exception to **clause 4.11.1(d)**.

4.11.4 The Tenant must comply with its obligations in **Schedule 5** when carrying out or installing any Permitted Works, whether or not the Landlord's consent is required for them.

4.11.5 Where the Landlord's consent is expressly required under this **clause 4.11**, the Landlord may impose requirements on the Tenant in addition to those contained in **Schedule 5** when giving its consent.

4.11.6 The Tenant has no rights to carry out any alterations, works or installations outside the Premises unless it is expressly permitted to do so by this Lease. If the Landlord, in its absolute discretion, permits alterations, works or installations outside the Premises that are not permitted by this Lease, those alterations, works or installations will then be treated as External Works.

4.11.7 The Tenant may, with the Landlord's consent, carry out works outside the Premises:

(a) to install or erect Plant on the Plant Area of a size and design approved by the Landlord; and

(b) to install new Conducting Media within the Building along routes approved by the Landlord to connect the Premises to any Plant installed or erected by the Tenant under **clause (a)**.

4.12 **Relocation of External Works** TC "4.12 Relocation of External Works" \l 2

4.12.1 The Tenant must relocate any External Works when requested to do so on reasonable notice being not less than one month's notice by the Landlord (or immediately in case of emergency) to such alternative location as the Landlord shall (acting reasonably) allocate.

4.12.2 The Landlord will be responsible for the Tenant's costs and expenses in complying with the Landlord's request to relocate the External Works unless their relocation is required only temporarily to enable the Landlord to carry out any of the Services and the costs will be included in the Service Costs.

4.13 **Signs and advertisements** TC "4.13 Signs and advertisements" \l 2

The Tenant must not display any signs or advertisements on the Premises that are visible from outside the Building or the Common Parts except, in either case, for business signs that indicate the Tenant's trading name in the style of and consistent with the Tenant's standard business signage that are visible only through the main entrance to the Premises.

4.14 **Obligations at the End Date** TC "4.14 Obligations at the End Date" \l 2

4.14.1 By the End Date the Tenant must have removed at its own cost:

(a) all tenant's and trade fixtures from the Premises;

(b) all Electronic Communications Apparatus and apparatus relating to Wireless Data Services installed by the Tenant or any undertenant at the Premises;

(c) all signage installed by the Tenant or any undertenant at the Premises or elsewhere on the Building;

(d) unless and to the extent that the Landlord notifies the Tenant not to do so not more than nine months and not less than three months before the End Date, all Permitted Works; and

(e) without affecting any of the Landlord's other rights, any works that have been carried out by the Tenant in breach of any obligation in this Lease.

4.14.2 The Tenant must, to the Landlord's reasonable satisfaction, make good all damage to the Premises or the Building caused when complying with **clause 4.14.1** and restore them to the same configuration, state and condition set out in the Base Build Specification annexed at **Appendix 1**.

4.14.3 At the End Date the Tenant must:

(a) give back the Premises (and the fixtures, plant and equipment in them) in good decorative order and in a state, condition and working order consistent with the Tenant's obligations in this Lease;

(b) give back the Premises with vacant possession; and

(c) hand to the Landlord any registers or records maintained by the Tenant pursuant to any statutory duty that relate to the Premises including any health and safety file, EPC and asbestos survey.

4.14.4 If the Tenant has not removed all of its property from the Premises by the End Date and the Landlord gives the Tenant not less than five Business Days' notice of its intention to do so:

(a) the Landlord may dispose of that property as the agent of the Tenant;

(b) the Tenant must indemnify the Landlord against any liability of the Landlord to any third party whose property has been disposed of in the genuine but mistaken belief that it belonged to the Tenant; and

(c) the Landlord must pay to the Tenant the proceeds of the disposal after deducting the costs of transportation, storage and disposal incurred by the Landlord.

4.15 **User** TC "4.15 User" \l 2

4.15.1 The Tenant must not use the Premises other than for the Permitted Use during the Permitted Hours.

4.15.2 The Tenant must not use the Premises for any illegal or immoral purpose, as a betting office, an amusement arcade or in connection with gaming, as offices to which members of the public are admitted, for any political or campaigning purposes or for any sale by auction.

4.15.3 The Tenant must not use the Premises for the sale of alcohol for consumption on or off the Premises or for the preparation or cooking of food other than, in either case, in connection with staff and client catering facilities ancillary to the Permitted Use.

4.15.4 The Tenant must not:

(a) keep in the Premises any plant, machinery or equipment (except that properly required for the Permitted Use) or any petrol or other explosive or specially flammable substance;

(b) cause any nuisance or damage to the Landlord or the other tenants or occupiers of the Building or to the owners, tenants or occupiers of any adjoining premises;

(c) overload any part of the Premises or the Building or any plant, machinery, equipment or Conducting Media;

(d) do anything that blocks the Conducting Media or makes them function less efficiently including any blockage to or corrosion of any drains, pipes or sewers by virtue of any waste, grease or refuse deposited by the Tenant or any cleaning of them carried out by the Tenant; or

(e) operate any apparatus so as to interfere with the lawful use of Electronic Communications Apparatus or the provision of Wireless Data Services elsewhere in the Building or on any adjoining premises.

4.15.5 When exercising any right granted to it for entry to any other part of the Building the Tenant must:

(a) cause as little damage and interference as is reasonably practicable to the remainder of the Building and the business of its tenants and occupiers and make good any physical damage caused to the Landlord's reasonable satisfaction; and

(b) comply with the Landlord's requirements and those of any other tenants and occupiers of the Building who are affected.

4.15.6 When exercising any right granted to it for entry to the Podium the Tenant must:

(a) not cause any damage to the Podium; and

(b) comply with the Landlord's requirements concerning the use of the Podium.

4.15.7 The Tenant must provide the Landlord with the names, addresses and telephone numbers of not fewer than two people who from time to time hold keys and any security access codes to the Premises and who may be contacted in an emergency if the Landlord needs access to the Premises outside the Tenant's normal business hours.

4.15.8 The Landlord gives no warranty to the Tenant that the Permitted Use is or will remain a lawful or permitted use for the Premises under planning legislation.

4.16 **Dealings with the Premises** TC "4.16 Dealings with the Premises" \l 2

4.16.1 The Tenant must not assign, underlet, charge, hold on trust, part with or share possession or occupation of the Premises in whole or in part or enter into any agreement to do so, except as authorised under this **clause 4.16** or **Schedule 6**.

4.16.2 The Tenant may, with the Landlord's consent, assign the whole of the Premises.

4.16.3 For the purposes of section 19(1A) of the Landlord and Tenant Act 1927:

(a) if reasonable required by the Landlord any consent to assign may be subject to a condition that:

(i) the assigning tenant gives the Landlord an AGA; and

(ii) any guarantor of the assigning tenant gives the Landlord a guarantee that the assigning tenant will comply with the terms of the AGA

in each case in a form that the Landlord requires, given as a deed and delivered to the Landlord before the assignment;

(b) any consent to assign may (to the extent required by the Landlord) be subject to either or both of the following conditions:

(i) that a guarantor (approved by the Landlord) that is not a Current Guarantor guarantees the assignee's performance of the Tenant's obligations in this Lease; and

(ii) the assignee enters into a rent deposit deed with the Landlord providing for a deposit of not less than nine months' Main Rent (plus VAT) (calculated as at the date of the assignment) as security for the assignee's performance of the tenant's covenants in this Lease with a charge over the deposit;

in either case in a form that the Landlord requires, given as a deed and delivered to the Landlord before the assignment;

(c) the Landlord may refuse consent to assign if:

(i) the Tenant has not paid in full all Rents and other sums due to the Landlord under this Lease that are not the subject of a legitimate dispute about their payment;

(ii) the accounts of the proposed assignee or its guarantor have not been audited or, if they have been audited, relate to a period or periods the most recent of which expired more than eleven months before the date of the application for consent to assignment;

(iii) the proposed assignee or its guarantor is a company incorporated in or an individual resident in a country outside the United Kingdom and there is no treaty for the mutual enforcement of judgments between the United Kingdom and that country unless, in relation to a company, it carries on and maintains a business in the United Kingdom and, in the opinion of the Landlord, it has sufficient assets in the United Kingdom to enable it to meet its liabilities under this Lease;

(iv) the proposed assignee or its guarantor is a person who enjoys sovereign or state immunity, unless a department, body or agency of the United Kingdom Government;

(v) the proposed assignee is a Group Company of the Tenant; or

(vi) the proposed assignee is a Current Guarantor;

(d) the Landlord may refuse consent to assign in any other circumstances where it is reasonable to do so; and

(e) the Landlord may require any other condition to the Landlord's consent if it is reasonable to do so.

4.16.4 The provisions of **Schedule 6** apply to underlettings of the Premises and the Tenant must comply with its obligations in that Schedule.

4.16.5 The Tenant may charge the whole of the Premises to a genuine lending institution without the Landlord's consent but the Tenant must notify the Landlord under **clause** 4.17 of any charge created.

4.16.6 In addition to the provisions of this **clause 4.16**, the Tenant may share occupation of the Premises with a Group Company of the Tenant on condition that:

(a) the Tenant notifies the Landlord of the identity of the occupier and the part of the Premises to be occupied;

(b) no relationship of landlord and tenant is created or is allowed to arise;

(c) the sharing of occupation ends if the occupier is no longer a Group Company of the Tenant; and

(d) the Tenant notifies the Landlord promptly when the occupation ends.

4.17 **Registration of dealings** TC "4.17 Registration of dealings" \l 2

4.17.1 The Tenant must provide the Landlord with a certified copy of every document transferring or granting any interest in the Premises (and, if relevant, evidence that sections 24 to 28 of the 1954 Act have been lawfully excluded from the grant of any interest) within one month after the transfer or grant of that interest.

4.17.2 The Tenant must, on request, supply details to the Landlord of the names and addresses of anyone in occupation of the Premises, whether they are in occupation for the purpose of carrying on a business, the areas they occupy, the rents paid and the terms upon which they are in occupation.

4.18 **Marketing** TC "4.18 Marketing" \l 2

4.18.1 Unless genuine steps are being taken towards renewal of this Lease, the Tenant must, during the six months before the End Date, allow the Landlord to:

(a) place on the Premises (but not obstructing the Tenant's corporate signage) a notice for their disposal; and

(b) subject to giving the Tenant reasonable notice of the same show the Premises at reasonable times in the day to potential tenants (who must be accompanied by the Landlord or its agents).

4.18.2 Subject to giving the Tenant reasonable notice of the same the Tenant must allow the Landlord at reasonable times in the day to show the Premises to potential purchasers of the Building (who must be accompanied by the Landlord or its agents).

4.19 **Notifying the Landlord of notices or claims** TC "4.19 Notifying the Landlord of notices or claims" \l 2

The Tenant must notify the Landlord as soon as reasonably practicable after the Tenant receives or becomes aware of any notice or claim affecting the Premises.

4.20 **Comply with Acts** TC "4.20 Comply with Acts" \l 2

4.20.1 The Tenant must do everything required under and must not breach any Act in respect of the Premises and their use and occupation and the exercise of the rights granted to the Tenant under this Lease.

4.20.2 The Tenant must not do or fail to do anything in respect of the Premises, the Building or their use and occupation the effect of which could make the Landlord liable to pay any penalty, damages, compensation, costs or charges under any Act.

4.20.3 The Tenant must promptly notify the Landlord of any defect or disrepair in the Premises that may make the Landlord liable under any Act or under this Lease.

4.21 **Planning Acts** TC "4.21 Planning Acts" \l 2

4.21.1 The Tenant must comply with the requirements of the Planning Acts and with all Planning Permissions relating to or affecting the Premises or anything done or to be done on them.

4.21.2 The Tenant must not apply for any Planning Permission except where any approval or consent required under any other provisions in this Lease for development or change of use has already been given and the Landlord has approved the terms of the application for Planning Permission.

4.21.3 The Tenant may only implement a Planning Permission that the Landlord has approved.

4.21.4 The Tenant must assume liability for and pay any Community Infrastructure Levy payable under Part 11 of the Planning Act 2008 or any other similar payments or liabilities that become due as a result of it (or its sub-tenants or other occupiers of the Premises) carrying out any Permitted Works or changing the use of the Premises. The Tenant will not be responsible under this Lease for any corresponding sums that become due as a result of

any permitted development to or change of use of the Building carried out by the Landlord or any other occupier of the Building.

4.22 **Rights and easements** TC "4.22 Rights and easements" \l 2

The Tenant must not knowingly allow any rights or easements to be acquired over the Premises. If an encroachment may result in the acquisition of a right or easement:

4.22.1 the Tenant must notify the Landlord; and

4.22.2 the Tenant must, at the Landlord's cost, help the Landlord in any way that the Landlord requests to prevent that acquisition.

4.23 **Management of the Building** TC "4.23 Management of the Building" \l 2

4.23.1 The Tenant must not load or unload vehicles except on the parts of the Building that it is permitted to use for that purpose by **paragraph 2 of Part 1 of Schedule 1**.

4.23.2 The Tenant must not park vehicles in the Common Parts except in any areas that it is permitted to use for that purpose by **paragraph 2** of **Part 1** of **Schedule 1**.

4.23.3 The Tenant must not obstruct the Podium or the Common Parts in any way or leave any goods on them.

4.23.4 The Tenant must not deposit rubbish anywhere on the Podium or the Building except in skips or bins provided for that purpose.

4.23.5 The Tenant must not use the Common Parts other than for the purposes designated under **clause 5.8**.

4.23.6 The Tenant must comply with all regulations notified to it or contained within any relevant tenant guide or handbook for the Building and/or the Podium published by the Landlord from time to time and provided to the Tenant. No regulations may impose obligations on the Tenant that are inconsistent with the Tenant's rights and obligations under this Lease.

4.24 **Superior interest** TC "4.24 Superior interest" \l 2

The Tenant must not breach any of the Landlord's obligations (excluding payment of rents or other sums) relating to the Building or the Podium in the Podium Leases or any obligations affecting the freehold interest in the Building or the Podium at the date of this Lease.

4.25 **Registration at the Land Registry** TC "4.25 Registration at the Land Registry" \l 2

4.25.1 If compulsorily registrable, the Tenant must:

(a) as soon as reasonably practicable following the date of this Lease, apply to register and then take reasonable steps to complete the registration of this Lease and the Tenant's rights at the Land Registry; and

(b) provide the Landlord with an official copy of the registered title promptly after receipt.

4.25.2 The Tenant must as soon as reasonably practicable (and in any event within 6 weeks) after the End Date, apply to the Land Registry to close and then take reasonable steps to complete the closure of any registered title relating to this Lease and to remove from the Landlord's registered title(s) to the Building and the Podium any reference to this Lease and the Tenant's rights.

4.26 **Applications for consent or approval** TC "4.26 Applications for consent or approval" \l 2

Where the Tenant makes any application to the Landlord for consent or approval under this Lease, the Tenant must provide the Landlord with a complete and accurate copy of the heads of terms for any proposed dealing (if applicable) and all plans, drawings, specifications, documents and any other information required by the Landlord.

5. **LANDLORD'S OBLIGATIONS** TC "5 LANDLORD'S OBLIGATIONS" \l 1

5.1 **Quiet enjoyment** TC "5.1 Quiet enjoyment" \l 2

The Tenant may peaceably hold and enjoy the Premises during the Term without any interruption by the Landlord or any person lawfully claiming under or in trust for the Landlord except as permitted by this Lease.

5.2 **Insurance** TC "5.2 Insurance" \l 2

The Landlord must comply with the Landlord's obligations in **Schedule 4**.

5.3 **Services** TC "5.3 Services" \l 2

The Landlord must comply with its obligations in **Part 2 of Schedule 3**.

5.4 **Repayment of rent** TC "5.4 Repayment of rent" \l 2

5.4.1 The Landlord must refund any Main Rent and Insurance Rent paid in advance by the Tenant in relation to the period falling after the End Date within 10 Business Days after the End Date.

5.4.2 **Clause 5.4.1** will not apply if the Landlord ends this Lease under **clause 6.1** or if this Lease is disclaimed by the Crown or by a liquidator or trustee in bankruptcy of the Tenant.

5.5 **Entry Safeguards** TC "5.5 Entry Safeguards" \l 2

The Landlord must, when entering the Premises to exercise any Landlord's rights:

5.5.1 give the Tenant at least three Business Days' prior notice (except in the case of emergency, when the Landlord must give as much notice as may be reasonably practicable);

5.5.2 where required by the Tenant, be accompanied by the Tenant's representative but the Tenant must make that representative available; and

5.5.3 repair any physical damage that the Landlord causes as soon as reasonably practicable.

5.6 **Scaffolding** TC "5.6 Scaffolding" \l 2

5.6.1 The Landlord must ensure that in relation to any scaffolding erected outside the Premises in exercise of the Landlord's rights under this Lease:

(a) it must (except in emergency when no notice need be given) give the Tenant not less than one month's prior written notice of its proposals;

(b) it is removed as soon as reasonably practicable, with any damage caused to the exterior of the Premises made good;

(c) it causes as little obstruction as is reasonably practicable to the entrance to the Premises.

5.6.2 If the Tenant's business signage is obstructed or interfered with by the scaffolding, the Landlord will permit the Tenant to display a sign (approved by the Landlord) on the exterior of the scaffolding in front of the Premises so that it is visible to the public.

5.7 **Podium Leases** TC "5.7 Podium Leases" \l 2

The Landlord must pay the rent reserved by the Podium Leases and comply with those tenant's obligations in the Podium Leases that are not the responsibility of the Tenant under this Lease.

5.8 **Designation of Common Parts and use of rights** TC "5.8 Designation of Common Parts and use of rights" \l 2

5.8.1 The Common Parts designated by the Landlord for the Tenant's use under **Part 1 of Schedule 1** must include those Common Parts that are from time to time necessary for the use and enjoyment of the Premises for their intended use.

5.8.2 If the Landlord does not designate specific Common Parts for the Tenant's use, the Tenant will be entitled to use all Common Parts that are from time to time necessary for the reasonable and proper enjoyment of the Premises for their intended use but the Tenant will not have the right to use any Common Parts used solely by the Landlord for the provision of the Services.

5.8.3 Any service risers allocated by the Landlord for the Tenant's use under **paragraph 1.2 of Part 1 of Schedule 1** must take into account the location of the Premises and the requirements of the Tenant but, when allocating service risers, the Landlord (acting reasonably) will be entitled to take into account its own requirements and the requirements of other tenants and occupiers of the Building for the use of the service risers.

5.8.4 The Landlord (acting reasonably) may manage the allocation of the roof space over which the Tenant is granted rights under **paragraph 5 of Part 1 of Schedule 1** taking into account its own requirements and the requirements of other tenants and occupiers of the Building. Where reasonably possible, areas will be separate for each tenant and the Landlord will take into account any riser allocation strategy and the location of the tenants' facilities requiring connection to those areas.

6. **AGREEMENTS** TC "6 AGREEMENTS" \l 1

6.1 **Landlord's right to end this Lease** TC "6.1 Landlord's right to end this Lease" \l 2

6.1.1 If any event listed in **clause 6.1.2** occurs, the Landlord may at any time afterwards re-enter the Premises or any part of them and this Lease will then immediately end.

6.1.2 The events referred to in **clause 6.1.1** are as follows:

(a) any of the Rents are unpaid for 21 days after becoming due whether or not formally demanded;

(b) the Tenant materially breaches this Lease;

(c) any 1925 Act, administrative, court-appointed or other receiver or similar officer is appointed over the whole or any part of the Tenant's assets, or the Tenant enters into any scheme or arrangement with its creditors in satisfaction or composition of its debts under the 1986 Act;

(d) if the Tenant is a company or a limited liability partnership:

(i) the Tenant enters into liquidation within the meaning of section 247 of the 1986 Act;

(ii) the Tenant is wound up or a petition for winding up is presented against the Tenant that is not dismissed or withdrawn within 14 days of being presented;

(iii) a meeting of the Tenant's creditors or any of them is summoned under Part I of the 1986 Act;

(iv) a moratorium in respect of the Tenant comes into force under section 1(A) of and schedule A1 to the 1986 Act;

(v) an administrator is appointed to the Tenant; or

(vi) the Tenant is struck off the register of companies;

(e) if the Tenant is a partnership, it is subject to an event similar to any listed in **clause 6.1.2(d)** with appropriate modifications so as to relate to a partnership;

(f) if the Tenant is an individual:

(i) a receiving order is made against the Tenant;

(ii) an interim receiver is appointed over or in relation to the Tenant's property;

(iii) the Tenant becomes bankrupt or the Tenant is the subject of a bankruptcy petition;

(iv) the Tenant is adjudicated bankrupt by an adjudicator pursuant to section 263I of the 1986 Act;

(v) the Tenant applies for or becomes subject to a debt relief order or the Tenant proposes or becomes subject to a debt management plan; or

(vi) an interim order is made against the Tenant under Part VIII of the 1986 Act or the Tenant otherwise proposes an individual voluntary arrangement;

(g) any event similar to any listed in **clauses 6.1.2(c) to 6.1.2(f)** occurs in relation to any guarantor of the Tenant's obligations under this Lease; or

(h) any event similar to any listed in **clauses 6.1.2(c) to 6.1.2(g)** occurs in any jurisdiction (whether it be England and Wales, or elsewhere).

6.1.3 Neither the existence nor the exercise of the Landlord's right under **clause 6.1.1** will affect any other right or remedy available to the Landlord.

6.1.4 In this **clause 6.1** references to "the Tenant", where the Tenant is more than one person, include any one of them.

6.2 **No acquisition of easements or rights** TC "6.2 No acquisition of easements or rights" \l 2

6.2.1 Unless they are expressly included in **Part 1 of Schedule 1**, the grant of this Lease:

(a) does not include any liberties, privileges, easements, rights or advantages over the Building or the Podium or any adjoining premises; and

(b) excludes any rights arising by the operation of section 62 of the 1925 Act or the rule in *Wheeldon v Burrows*.

6.2.2 The Tenant has no rights that would restrict building or carrying out of works to the Building or the Podium or any adjoining premises, other than any that the Landlord specifically grants the Tenant in this Lease.

6.2.3 The flow of light to the Premises is and will be enjoyed with the Landlord's consent in accordance with section 3 of the Prescription Act 1832. Neither the enjoyment of that light and air nor anything in this Lease will prevent the exercise of any of the rights the Landlord has reserved out of this Lease. The Tenant must permit the exercise of these reserved rights without interference or objection.

6.2.4 The Tenant must not do or omit to do anything that would or might result in the loss of any right enjoyed by the Premises or the Building or the Podium.

6.2.5 The Tenant has no rights to enforce, release or modify or to prevent the release, enforcement or modification of, the benefit of any obligations, rights or conditions to which any other property within the Building or the Podium or any adjoining premises is or are subject.

6.3 **Service of Notices** TC "6.3 Service of Notices" \l 2

6.3.1 Any Notice must be in writing and sent by pre-paid first class post or special delivery to or otherwise delivered to or left at the registered office or, if they do not have a registered office, to the last known address in the United Kingdom of the recipient or to any other address in the United Kingdom that the recipient has specified as its address for service by giving not less than ten Business Days' notice under this **clause 6.3**. Any notice to be served on the Tenant may be sent by pre-paid first class or special delivery to or otherwise delivered to or left at the Premises.

6.3.2 Any Notice given will be treated as served on the second Business Day after the date of posting if sent by pre-paid first class post or special delivery or at the time the Notice is delivered to or left at the recipient's address if delivered to or left at that address. If a Notice is treated as served on a day that is not a Business Day or after 5.00pm on a Business Day it will be treated as served at 9.00am on the immediately following Business Day.

6.3.3 Service of a Notice by fax or e-mail is not a valid form of service under this Lease.

6.4 **Contracts (Rights of Third Parties) Act 1999** TC "6.4 Contracts (Rights of Third Parties) Act 1999" \l 2

Nothing in this Lease creates any rights benefiting any person under the Contracts (Rights of Third Parties) Act 1999.

6.5 **Contracting-out** TC "6.5 Contracting-out" \l 2

6.5.1 The Landlord and the Tenant confirm that before the date of the agreement for the grant of this Lease dated 23 November 2021 made between the parties to this Lease:

(a) a notice complying with Schedule 1 to the Regulatory Reform (Business Tenancies) (England and Wales) Order 2003 which relates to this tenancy was served by the Landlord on the Tenant on 19 November 2021; and

(b) a statutory declaration dated 19 November 2021 complying with paragraph 8 of Schedule 2 to that Order was made by or on behalf of the Tenant (and if the statutory declaration was made on behalf of the Tenant, the Tenant confirms that the declarant was duly authorised by the Tenant to make the statutory declaration on its behalf).

6.5.2 The Landlord and the Tenant agree and declare that the provisions of sections 24–28 (inclusive) of the 1954 Act do not apply to the tenancy created by this Lease.

6.6 **Energy Performance Certificates** TC "6.6 Energy Performance Certificates" \l 2

6.6.1 The Tenant must not obtain or commission an EPC in respect of the Premises unless required to do so by the Landlord for alterations or under the EPB Regulations. If the Tenant is required to obtain an EPC, the Tenant must notify the Landlord promptly following which (and subject to the Tenant paying the Landlord's costs of obtaining an EPC for the Premises) the Landlord shall obtain an EPC.

6.6.2 The Tenant must cooperate with the Landlord, so far as is reasonably necessary, to allow the Landlord to obtain any EPC for the Premises or the Building and:

(a) provide the Landlord with copies of any plans or other information held by the Tenant that would assist in obtaining that EPC; and

(b) allow such access to the Premises to any energy assessor appointed by the Landlord as is reasonably necessary to inspect the Premises for the purposes of preparing any EPC.

6.6.3 The Tenant shall supply promptly to the Landlord a copy of any EPC the Tenant or any undertenant obtains or commissions in respect of the Premises or the Building together with the energy modelling calculation file and supporting drawings (also known as the NCT file).

6.6.4 The Landlord must give the Tenant written details on request of the unique reference number of any EPC the Landlord obtains or commissions in respect of the Premises or the Building.

6.7 **Energy Efficiency and Data Sharing** TC "6.7 Energy Efficiency and Data Sharing" \l 2

6.7.1 The Landlord and the Tenant shall share the data they hold in respect of energy and water use and waste production/recycling as reasonably required between themselves and with any other third party who the parties agree needs to receive such data.

6.7.2 The Landlord and the Tenant shall keep the data disclosed under this provision confidential and shall only use such data for the purposes of ensuring that the Building is run in a sustainable way that minimises its environmental impact.

6.7.3 The Landlord shall ensure that similar restrictions on the publication and use of such data are placed on its managing agent and any other party responsible for the operation or management of the Building.

6.7.4 The Tenant shall co-operate with the Landlord in relation to any reasonable initiatives, in connection with the efficiency of the use of energy or water, the Environmental Performance or sustainability characteristics of the Building, including the EPC and BREEAM ratings provided that the parties shall have due regard to the costs associated with implementing any initiatives compared to the benefit to the Tenant of the outcome of any such initiatives.

6.7.5 Where the Premises are not already separately metered, the Landlord shall have the right to install separate sub-metering of utilities and/or heating and/or cooling used in the Premises. The Tenant shall give the Landlord the necessary access in order to allow for such metering to be installed. The Landlord shall give reasonable notice of the intention to install such metering and, when installing, shall use all reasonable endeavours not to disturb the Tenant's beneficial use and occupation of the Premises.

6.8 **Release of Landlord** TC "6.8 Release of Landlord" \l 2

The Landlord's obligations in this Lease will not bind the Landlord after it has disposed of its interest in the Premises and the Landlord will not be liable for any breach of the Landlord's obligations in this Lease arising after the date of that disposal.

6.9 **Superior landlord's consent** TC "6.9 Superior landlord's consent" \l 2

Any consent that the Landlord gives is conditional on the consent (where required) of any superior landlord being obtained. The Landlord will apply for that consent at the Tenant's cost and, to the extent the Landlord is consenting, the Landlord must take reasonable steps to obtain it.

6.10 **Limitations on title guarantee** TC "6.10 Limitations on title guarantee" \l 2

6.10.1 For the purposes of section 6(2) of the 1994 Act:

(a) all entries made in any public register that a prudent tenant would inspect will be treated as within the actual knowledge of the Tenant;

(b) section 6(3) of the 1994 Act will not apply; and

(c) the Tenant will be treated as having actual knowledge of any matters that would be disclosed by an inspection of the Premises.

6.10.2 Title to tenant's fixtures is excluded from the title guarantee.

6.10.3 The Tenant will be responsible for the Landlord's costs incurred in complying with the covenant set out in section 2(1)(b) of the 1994 Act.

7. **EXISTING CONTAMINATION** TC "7 EXISTING CONTAMINATION" \l 1

It is acknowledged and agreed between the Landlord and the Tenant that:

7.1 The Tenant has no liability under any of the terms of this Lease in respect of:

7.1.1 the presence in, on, under or over the Premises of any Hazardous Material on or prior to the date of this Lease; or

7.1.2 the migration or escape onto (whether before or on the date of this Lease) the Premises of any Hazardous Material from any adjoining or nearby premises;

7.2 Notwithstanding any other term of this Lease the Tenant will not be liable to remediate and will not be liable for any costs incurred by the Landlord in respect of any matter falling within **clause 7.1**; and

7.3 This acknowledgement is made in accordance with the relevant statutory guidance to exclude the Tenant and all persons deriving title through or under the Tenant, from liability as an appropriate person to bear responsibility for any costs and liability in respect of such matters.

8. **BREAK CLAUSE** TC "8 BREAK CLAUSE" \l 1

8.1 The Tenant may end the Term on the Break Date by giving the Landlord not less than 6 months' notice specifying the Break Date following which the Term will end on the Break Date if:

8.1.1 on the Break Date the Main Rent due up to and including that Break Date has been paid in full;

8.1.2 on the Break Date the whole of the Premises are given back to the Landlord free of the Tenant's occupation and the occupation of any other lawful occupier and without any continuing underleases; and

8.1.3 the Tenant has, on or before the Break Date, paid to the Landlord 25% of the annual Main Rent payable under **clause 3.2.2** (plus any VAT payable on that amount).

8.2 The Landlord may waive any of the pre-conditions in **clauses 8.1.1 to 8.1.3** at any time before the Break Date by notifying the Tenant.

8.3 If the Tenant gives notice to the Landlord under **clause 8.1**, the Tenant must on or before the Break Date make the payment to the Landlord as detailed in **clause 8.1.3**.

8.4 If this Lease ends under this **clause 7**, this will not affect the rights of any party for any prior breach of an obligation in this Lease.

8.5 Time is of the essence for the purposes of this **clause 7**.

9. **JURISDICTION** TC "9 JURISDICTION" \l 1

9.1 This Lease and any non-contractual obligations arising out of or in connection with it will be governed by the law of England.

9.2 Subject to **clause 9.3** and any provisions in this Lease requiring a dispute to be settled by an expert or by arbitration, the courts of England have exclusive jurisdiction to decide any dispute arising out of or in connection with this Lease, including in relation to any non-contractual obligations.

9.3 Any party may seek to enforce an order of the courts of England arising out of or in connection with this Lease, including in relation to any non-contractual obligations, in any court of competent jurisdiction.

10. **LEGAL EFFECT** TC "10 LEGAL EFFECT" \l 1

This Lease takes effect and binds the parties from and including the date at clause LR1.

1 SCHEDULE 1 TC "SCHEDULES" \L 4 \N

Rights TC "1 Rights" \l 3

Part 1 Tenant's Rights TC "Part 1 Tenant's Rights" \l 2

The following rights are granted to the Tenant in common with the Landlord, any person authorised by the Landlord and all other tenants and occupiers of the Building but subject to the Landlord's rights (it being acknowledged that the rights granted in this Lease over such parts of the Podium as are demised to the Landlord under each of the Podium Leases shall only subsist for so long as the relevant Podium Lease (or any replacement of such Podium Lease) subsists):

1. **Running of services**

1.1 To connect to and use the existing Conducting Media at the Building intended to serve the Premises for the passage of Supplies from and to the Premises.

1.2 To use a fair proportion of the riser space allocated to tenants for their use within the Building that the Landlord has designated for the purpose of installing and running new Conducting Media exclusively serving the Premises.

2. **Access and servicing**

2.1 Access to and from the Premises at all times on foot only over the Common Parts and all of the Podium (with the exception of that part of the Podium registered under title number BGL125422, in respect of which the Landlord shall only grant such right to the extent that the Landlord (under the terms of Landlord's lease of such land as referred to in the definition of the "Podium Leases") is legally entitled to do so).

2.2 Subject to **clause 4.23** to use each of the following within the Common Parts from time to time designated by the Landlord for the Tenant's use:

2.2.1 any service area for loading and unloading and otherwise servicing the Premises;

2.2.2 the service roads with or without vehicles to come and go to and from any service area specified in **paragraph 2.2.1**; and

2.2.3 the service corridors and any goods lifts with or without trolleys to come and go between the Premises and any service area specified in **paragraph 2.2.1**.

3. **Refuse disposal**

To deposit rubbish in any receptacles or waste compactors within the Common Parts and the Podium provided by the Landlord for that purpose and designated by the Landlord for the use of the Tenant.

4. **Entry onto the Common Parts**

4.1 If the relevant work cannot otherwise be reasonably carried out, to enter the Common Parts with or without workmen, plant, equipment and materials to comply with the Tenant's obligations in this Lease. When exercising this right, the Tenant must:

4.1.1 give the Landlord at least three Business Days' prior notice (except in the case of emergency, when the Tenant must give as much notice as may be reasonably practicable);

4.1.2 observe the Landlord's requirements (but where that includes being accompanied by the Landlord's representative the Landlord must make that representative available);

4.1.3 cause as little interference to the operation and use of the Building as reasonably practicable;

4.1.4 cause as little physical damage as is reasonably practicable;

4.1.5 repair any physical damage that the Tenant causes as soon as reasonably practicable;

4.1.6 where entering to carry out works, obtain the Landlord's approval to the location, method of working and any other material matters relating to the preparation for, and execution of, the works;

4.1.7 remain upon the Common Parts for no longer than is reasonably necessary; and

4.1.8 where practicable, exercise this right outside the normal business hours of the Building.

5. **Plant**

5.1 Subject to the Tenant complying with **clauses 4.10 and 4.12**, to erect and maintain wireless network equipment, television aerials and satellite dishes and plant on the roof of the Building in the Plant Area, of a size and design, and with connections to the Premises, approved by the Landlord.

5.2 Subject to the Landlord complying with **clause 5.8**, the Landlord may allocate alternative roof space to the Tenant at any time so long as the alternative roof space is not materially less commodious to the Tenant.

5.3 Nothing in this **paragraph 5** grants the Tenant rights to install any Electronic Communications Apparatus if the Tenant or the owner or operator of the Electronic Communications Apparatus would acquire rights to use and retain the Electronic Communications Apparatus under the Telecommunications Act 1984.

6. **Signage**

To exhibit the Tenant's name in such form, shape and size as the Landlord specifies as the standard size and form of such signs:

6.1 on any display board provided by the Landlord in the entrance lobby of the Building; and

6.2 in the Common Parts adjacent to the main entrance to the Premises.

7. **Support and shelter**

Support and shelter for the Premises from the Building.

8. **Staff cycle parking**

8.1 To park up to 30 bicycles within the following spaces:

8.1.1 2 yellow cycle rack spaces;

8.1.2 2 Brompton bike lockers; and

8.1.3 26 standard cycle rack spaces

within the Common Parts or the Podium.

8.2 To use up to 28 lockers comprising the following:

8.2.1 11 lockers within the gents shower room;

8.2.2 9 lockers within the ladies shower room; and

8.2.3 8 lockers within the cycle storage area,

within the Common Parts.

8.3 The Landlord may, by notice in writing to the Tenant, vary the location of the lockers and cycle spaces from time to time.

9. **Toilet facilities**

To use any toilet and shower facilities within the Common Parts designated by the Landlord as facilities for the use of the tenants of the Building.

10. **Communal Roof Terraces**

To use the communal roof terrace on the 10th floor of the Building designated by the Landlord as for the use of the tenants of the Building.

11. **Generator**

The exclusive use of 100Kva from the back-up generator at the Building.

12. **Escape**

On foot only, in emergencies and for fire escape drills, to use all fire escape routes:

12.1 in the Building as designated by the Landlord for the use of the tenants of the Building whether or not forming part of the Common Parts; and

12.2 across the Podium as designated by the Landlord for the use of the tenants of the Building.

13. **Staff Parking**

An exclusive right to park one (1) vehicle (such vehicle belonging to persons working at, or authorised visitors to, the Premises) within the parking space shaded red on Plan 6 (or such alternative parking space in any location within the Car Park notified by the Landlord to the Tenant (giving not less than two weeks' notice)).

Part 2 Landlord's Rights TC "Part 2 Landlord's Rights" \l 2

The following rights are excepted and reserved to the Landlord:

1. **Support, shelter, light and air**

1.1 Support and shelter for the remainder of the Building from the Premises.

1.2 All rights of light or air to the Premises that now exist or that might (but for this reservation) be acquired over any other land.

2. **Running of services**

2.1 The passage and running of Supplies from and to the remainder of the Building through existing Conducting Media (if any) within the Premises.

2.2 The right to install new Conducting Media within the Premises and connect to them for the passage and running of Supplies to and from the remainder of the Building and any adjoining premises.

3. **Entry on to the Premises**

3.1 To enter the Premises:

3.1.1 ascertain whether the Tenant has complied with its obligations under this Lease;

3.1.2 provide the Services;

3.1.3 estimate the current value or rebuilding cost of the Premises and the Building for insurance or any other purposes;

3.1.4 inspect and measure the Premises for any purpose connected with the review of the Main Rent or the renewal of this Lease;

3.1.5 inspect the state of repair and condition of the Premises and prepare any schedule of condition or dilapidations;

3.1.6 inspect, clean, maintain, replace or repair any existing Conducting Media within the Premises but serving the Building;

3.1.7 carry out any repairs, remove and make good any unauthorised alterations or carry out any works that the Tenant should have carried out under this Lease;

3.1.8 take schedules or inventories of landlord's fixtures and other items to be returned to the Landlord at the end of the Term;

3.1.9 show the Premises to prospective buyers of the Building or, during the last six months of the Term, to prospective tenants of the Premises;

3.1.10 carry out or permit the repair, maintenance, decoration, replacement, renewal and cleaning of any adjoining premises or any building or engineering works upon them; and

3.1.11 enable the production of an EPC for the Premises or the Building whether or not the Landlord is under a statutory duty to produce an EPC or undertaking an air conditioning inspection and, for such purposes, the right to carry out the necessary tests on equipment; and

3.1.12 review or measure the Environmental Performance of the Premises, including to install, inspect, clean, maintain, replace and to take readings from metering equipment, heat cost allocators and thermostatic radiator valves within or relating to the Premises.

3.2 If the relevant work cannot be reasonably carried out without entry onto the Premises, to enter them to:

3.2.1 build on or into any boundary or party walls on or adjacent to the Premises;

3.2.2 inspect, repair, alter, decorate, rebuild or carry out other works upon the Building; or

3.2.3 for any other reasonable management purpose.

3.3 To enter the Premises to do anything that the Landlord is expressly entitled or required to do under this Lease or for any other reasonable purpose in connection with this Lease.

4. **Common Parts and Conducting Media**

4.1 In an emergency, or when works are being carried out to them, to close off or restrict access to the Common Parts, so long as (except in an emergency) alternative facilities are provided that are not materially less convenient.

4.2 To change, end the use of or reduce the extent of the Podium, any Common Parts or Conducting Media so long as:

4.2.1 alternative facilities are provided that are not materially less convenient; or

4.2.2 if no alternative is provided, the use and enjoyment of the Premises is not materially adversely affected.

4.3 From time to time to designate areas within the Common Parts for particular purposes including as service areas, car parks, service roads and footpaths and from time to time to reduce the size of any designated areas, so long as the remaining areas are reasonably adequate for their intended purposes.

4.4 To run Conducting Media over, under or along those areas allocated for the use of the Tenant under **paragraph 5 of Part 1 of Schedule 1** (or allow others to do so) so long as they do not materially adversely affect the Tenant's use of those areas.

5. **Podium**

In an emergency, or when works are being carried out to them, or when any event takes place on the Podium, to close off or restrict access to the Podium provided that the Landlord shall re-open the Podium or remove such restriction as soon as reasonably practicable following such emergency, works or event.

6. **Adjoining premises**

To carry out works of construction, demolition, alteration or redevelopment on the Building, the Podium and any adjoining premises (and to permit others to do so) as the Landlord in its absolute discretion considers fit (whether or not these works interfere with the flow of light and air to the Premises) and the right in connection with those works to underpin and shore up the Premises.

7. **Plant, equipment and scaffolding**

The right, where necessary, to bring plant and equipment onto the Premises and to place scaffolding and ladders upon the exterior of or outside any buildings on the Premises and/or the Podium in exercising the Landlord's rights (and/or undertaking the Landlord's obligations) under this Lease.

2 SCHEDULE 2

Rent review TC "2 Rent review" \l 3

1. **Defined terms**

This **Schedule 2** uses the following definitions:

"**Assumptions**"

that:

(a) if the Building, the Podium or any part of them have been damaged or destroyed, they have been reinstated before the Rent Review Date;

(b) the Building is accessible and has the benefit of all essential services;

(c) the Podium is accessible and the rights contained in this Lease which relate to the Podium may lawfully be exercised;

(d) the Premises are fit for immediate occupation and ready to receive the willing tenant's fitting-out works;

(e) the Premises may lawfully be let to, and used for the Permitted Use by, any person throughout the term of the Hypothetical Lease;

(f) there are no breaches of the Landlord's or Tenant's obligations in this Lease; and

(g) on the grant of the Hypothetical Lease the willing tenant will receive the benefit of a rent free period, rent concession or any other inducement of a length or amount that might be negotiated in the open market for fitting-out purposes and that the Market Rent is the rent that would become payable after the end of that period or concession or payment of that inducement.

"**Disregards**"

any or all of the following:

(a) any effect on rent of the Tenant (and the Tenant's predecessors in title and lawful occupiers) having been in occupation of the Premises;

(b) any goodwill accruing to the Premises because of the Tenant's business (and that of the Tenant's predecessors in title and lawful occupiers);

(c) any special bid that the Tenant or any other party with a special interest in the Premises might make by reason of its occupation of any other part of the Building or any adjoining premises;

(d) any increase in rent attributable to any improvement, including any tenant's initial fitting-out works, whether or not within the Premises:

(i) carried out by and at the cost of the Tenant or the Tenant's predecessors in title or lawful occupiers before or during the Term;

(ii) carried out with the written consent, where required, of the Landlord or the Landlord's predecessors in title; and

(iii) not carried out pursuant to an obligation to the Landlord or the Landlord's predecessors in title (but any obligations relating to the method or timing of works in any document giving consent will not be treated as an obligation for these purposes);

(e) any reduction in rent attributable to works that have been carried out by the Tenant (or the Tenant's predecessors in title or lawful occupiers); and

(f) any reduction in rent attributable to any temporary works, operations or other activities on any adjoining premises.

"**Hypothetical Lease**"

a single lease:

(a) of the whole of the Premises;

(b) on the same terms as this Lease (including this **Schedule 2**) except for:

(i) the amount of Main Rent reserved immediately before the Rent Review Date;

(ii) any rent free period, rent concession or any other inducement received by the Tenant in relation to the grant of this Lease; and

(iii) any break clause in this Lease;

(c) by a willing landlord to a willing tenant;

(d) with vacant possession;

(e) without any premium payable by or (subject to **paragraph (g**) of the definition of "Assumptions") to either the willing tenant or the willing landlord;

(f) for a term of 10 years starting on the Rent Review Date;

(g) with rent review dates every five years; and

(h) with a right for the tenant to bring the Hypothetical Lease to an end on the fifth anniversary of the date on which the term starts.

"**Market Rent**"

the yearly rent at which the Premises might reasonably be expected to be let on the open market on the Rent Review Date, on the terms of the Hypothetical Lease and applying the Assumptions and the Disregards.

2. **Rent review**

2.1 On the Rent Review Date the Main Rent is to be reviewed to the higher of:

2.1.1 the Main Rent reserved immediately before the Rent Review Date; and

2.1.2 the Market Rent.

2.2 The reviewed Main Rent will be payable from and including the Rent Review Date.

3. **Resolution of disputes**

3.1 The Market Rent at the Rent Review Date may be agreed between the Landlord and the Tenant. If they have not done so (whether or not they have tried) by the date three months before the Rent Review Date, either the Landlord or the Tenant can require the Market Rent to be decided by an independent expert. If the Landlord and the Tenant do not agree on who should decide the Market Rent, the expert will be appointed by the President of the Royal Institution of Chartered Surveyors on the application of either the Landlord or the Tenant. The expert will:

3.1.1 invite the Landlord and the Tenant to submit to him a proposal for the Market Rent with any relevant supporting documentation;

3.1.2 give the Landlord and the Tenant an opportunity to make counter submissions;

3.1.3 give written reasons for his decisions, which will be binding on the parties; and

3.1.4 be paid by the Landlord and the Tenant in the shares and in the manner that he decides (or failing a decision, in equal shares).

3.2 The expert must be an independent chartered surveyor of not less than ten years' standing who is experienced in the rental valuation of property similar to the Premises and who knows the local market for such premises.

3.3 If the expert dies, becomes unwilling or incapable of acting or it becomes apparent for any other reason that he will be unable to decide the Market Rent within a reasonable time, he may be replaced by a new expert who must be appointed on the terms set out in this **paragraph** 3.

3.4 Responsibility for the costs of referring a dispute to an expert, including costs connected with the appointment of the expert but not the legal and other professional costs of any party in relation to a dispute, will be decided by the expert and failing a decision, they will be shared equally between the parties.

4. **Consequences of delay in agreeing the revised rent**

4.1 If, by the Rent Review Date, the reviewed Main Rent has not been ascertained, then:

4.1.1 the Main Rent reserved under this Lease immediately before the Rent Review Date will continue to be payable until the reviewed Main Rent has been ascertained;

4.1.2 following the ascertainment of the Main Rent, the Landlord will demand the difference (if any) between the amount the Tenant has actually paid and the amount that would have been payable had the Main Rent been ascertained before the Rent Review Date; and

4.1.3 the Tenant must pay that difference to the Landlord within 10 Business Days after that demand and interest at three per cent below the Interest Rate calculated on a daily basis on each instalment of that difference from the date on which each instalment would have become payable to the date of payment. If not paid those sums will be treated as rent in arrear.

5. **Rent review memorandum**

When the Market Rent has been ascertained, a memorandum recording the Main Rent reserved on review must be entered into. The Landlord and the Tenant will each bear their own costs in relation to that memorandum.

6. **Time not of the essence**

For the purpose of this **Schedule 2** time is not of the essence.

3 SCHEDULE 3

Services and Service Charge TC "3 Services and Service Charge" \l 3

Part 1 Administrative provisions TC "Part 1 Administrative provisions" \l 2

1. **Accounting period**

The accounting period will be the period ending on 30 June in each year or otherwise as the Landlord may decide and notify to the Tenant. For any accounting period that does not fall wholly within the Term, the Service Charge will be a due proportion calculated on the assumption that the service charge expenditure accrues equally on a day to day basis throughout the period.

2. **Service charge statements**

2.1 After the end of each accounting period, the Landlord will supply the Tenant with a statement (the **"Service Charge Statement"**) for that accounting period of the:

2.1.1 Service Costs; and

2.1.2 Service Charge payable.

2.2 The Landlord must take reasonable steps to supply the Service Charge Statement within four months after the end of each accounting period.

2.3 Service Costs incurred in one accounting period, if not included in the Service Charge Statement for that accounting period for any reason, may be included in the Service Charge Statement for a subsequent accounting period.

2.4 The Tenant will be entitled upon prior appointment to inspect evidence of the Service Costs at the Landlord's head office or any other location the Landlord specifies. The Tenant must ask to inspect the evidence not later than four months after receipt of the Service Charge Statement.

3. **On-account payments of service charge**

3.1 Until the Service Charge for each accounting period has been calculated, the Tenant must pay, by equal quarterly payments on the Rent Days, a provisional sum by way of Service Charge at the level that the Landlord requires.

3.2 The Tenant must also pay on demand any sum or sums that the Landlord requires where the Landlord will be obliged to incur any Service Costs and the sums held on account by the Landlord are insufficient to meet those costs.

3.3 The Landlord may, at the Landlord's option, either recover the costs of providing heating and cooling to the Premises from the Tenant in accordance with **clause 4.2** or as part of the Service Charge in accordance with this **paragraph 3 of Part 1** of this Schedule.

4. **Balancing payments of service charge**

4.1 When the Service Charge for each accounting period has been calculated:

4.1.1 the Tenant must pay any amount due from it on demand; and

4.1.2 the Landlord must credit any amount due to the Tenant against the next payment or payments to be made by the Tenant under **paragraph 3 of Part 1** of this Schedule. Any amount owing at the End Date must be repaid to the Tenant within one month of its calculation.

4.2 The End Date will not affect the Tenant's obligation to pay or the Landlord's right to recover Service Charge after the End Date where this has not been calculated and demanded before the End Date.

5. **Service charge disputes**

If any dispute arises in connection with the Service Charge, the Landlord and the Tenant must attempt to resolve it by appropriate alternative means before resorting to court proceedings. The Service Charge Statement will (except for obvious error) become binding on the parties four months after it is delivered to the Tenant or (if later) once any dispute relating to it and arising during that period has been settled or decided.

6. **Variation in the proportion of the service charge payable**

6.1 In calculating the Service Charge for any of the Services, the Landlord's surveyor may make any adjustment that is fair and reasonable in all the circumstances, having regard to the relative degree of benefit obtained by the Tenant and other tenants at the Building from those Services, including by dividing the services and charges set out in **Part 3 of this Schedule** into separate categories and applying weighting to those categories to take into account differing uses or operating hours.

6.2 If there is any change in the extent of the Building or the Podium, the Landlord must, where it is appropriate to do so, vary the Service Charge as is reasonable to take account of that change but the Service Charge will not materially increase solely as a result of any change in the extent of the Building.

6.3 The Service Charge must not be increased by reason only that any Lettable Units:

6.3.1 remain unlet;

6.3.2 are let on terms that do not require the tenant or other occupier to pay a service charge; or

6.3.3 are let on terms that cap the liability of any tenant or other occupier for service charge.

7. **Landlord's contribution to service charge**

7.1 The Landlord is to contribute to the Service Charge any shortfall in the Service Charge arising from any Lettable Units:

7.1.1 being unlet;

7.1.2 are let on terms that do not require the tenant or other occupier to pay a service charge; or

7.1.3 are let on terms that cap the liability of any tenant or other occupier for service charge where the level of the service charge attributed to the relevant area exceeds the cap.

Part 2 Landlord's obligations TC "Part 2 Landlord's obligations" \l 2

1. **Provision of services**

1.1 The Landlord, acting reasonably and in the interests of good estate management:

1.1.1 may supply the Services listed in **paragraph 23 of Part 3**;

1.1.2 must supply all or any of the remaining Services listed in **Part 3** in an efficient manner at all appropriate times; and

1.1.3 may vary, reduce or extend those Services.

2. **Landlord's rights and responsibilities**

2.1 The Landlord:

2.1.1 may from time to time employ such agents, contractors or others as the Landlord decides; and

2.1.2 will not be responsible for any interruption in the supply of the Services due to any circumstances outside the Landlord's control or due to any necessary maintenance, repair, replacement, renewal, servicing, inspection or testing, but must take reasonable steps to restore the supply as soon as reasonably practicable.

Part 3 Services and charges TC "Part 3 Services and charges" \l 2

1. Repairing (and by way of repair, renewing, rebuilding and replacing), decorating, maintaining and cleaning the foundations, roof, structure and exterior of the Building and all Common Parts, Conducting Media and the Podium.

2. Repairing (and, by way of repair, renewing, rebuilding, and replacing), decorating, maintaining and cleaning any facilities (including means of access, Conducting Media, party walls and other boundary structures) used in common between the Building and any adjoining premises.

3. Repairing (and, by way of repair, renewing, rebuilding, and replacing), decorating, maintaining and cleaning any facilities (including means of access, Conducting Media, party walls and other boundary structures) affecting the Podium.

4. The costs of cleaning the external surfaces of the window and window frames in the Building and providing and maintaining plant, facilities and equipment for these purposes.

5. Lighting, heating, providing air-conditioning to and ventilating the Common Parts.

6. Lighting the Podium, the exterior of the Building and any facilities used in common between the Building and any adjoining premises.

7. Providing hot and cold water to, and maintaining operational supplies in, the toilets in the Common Parts.

8. Supply Costs incurred in providing the Services.

9. All existing and future rates, taxes, duties, charges and financial impositions charged on:

9.1 the Podium; and

9.2 the Common Parts or the Building as a whole,

(and a fair proportion of those levied on the Building along with any adjoining premises).

10. Providing, inspecting, maintaining (including by maintenance contracts and insurance against sudden and unforeseen breakdown), repairing, renewing, replacing, upgrading and operating:

(a) all plant, machinery, apparatus and vehicles used in providing the Services and all signage in the Common Parts and on the Podium; and

(b) security, fire-fighting and fire-detection equipment (excluding portable fire extinguishers in the Premises), fire alarm systems, public address systems, telecommunications systems, closed circuit television systems and traffic control and all other Building Management Systems.

11. Employing or procuring all staff (including remuneration, incidental benefits and all associated costs and overheads) for the management and security of the Building and of the Podium and otherwise in connection with the Services.

12. Providing non-residential accommodation for staff, plant, furniture, equipment and vehicles used in providing the Services, and all outgoings on them.

13. Employing or procuring agents, contractors or others as the Landlord decides in connection with the Services.

14. Storing, compacting, recycling and disposing of refuse.

15. Planting, replanting and maintaining landscape features in the Common Parts and on the Podium.

16. Providing, cleaning and renewing carpeting in the Common Parts.

17. Providing reception facilities for visitors to the Building.

18. Pest and infection control.

19. Gritting, and clearing snow from, the Common Parts and the Podium.

20. Providing seasonal decorations within the Building.

21. Carrying out any works and providing and maintaining all facilities that are required under any Act or by insurers in relation to the Building and/or the Podium.

22. Providing any further services for maintaining and securing the amenities of the Building and/or the Podium.

23. Encouraging and procuring such services, amenities and events (including the arts, culture, creativity and commerce) in the Building and on the Podium so as to strengthen the connection between the occupiers of the Building, the people in the buildings surrounding the Podium, and the local population.

24. The payment of the amount of any excess or deductible under any insurance policy as referred to in **paragraph 1.1.1(d) of Schedule 4** (to the extent that the Landlord does not recover such amounts under that paragraph).

25. Managing and administering service charge accounts for the Services and the Building including, where relevant, certifying, examining or auditing those accounts.

26. Auditing health and safety requirements for the Building and Podium and, where required by law or reasonable and cost-effective to do so, implementing the recommendations of that audit.

27. Auditing disabled access requirements for the Building and the Podium and, where required by law or reasonable and cost-effective to do so, implementing the recommendations of that audit.

28. Auditing the Environmental Performance of the Building and, where reasonable and cost-effective to do so, implementing the recommendations of any environmental management plan the Landlord has for the Building from time to time.

29. Interest costs reasonably incurred by the Landlord on borrowing from a UK clearing bank or, if the Landlord uses its own moneys, an amount equal to the interest costs that would have been incurred if the Landlord had borrowed from a UK clearing bank at reasonable commercial rates. Interest costs will be reasonably incurred under this paragraph if:

    (a) the Landlord has to meet an immediate liability where the service charge funds held by the Landlord are insufficient for that purpose and the shortfall does not result from any caps on the amount of service charge recoverable, any non-payment of service charges by other tenants or any unlet Lettable Unit; or

    (b) the Landlord decides at its absolute discretion to incur service charge expenditure in one accounting period and recover that expenditure over two or more accounting periods.

Part 4 Service Charge Exclusions TC "Part 4 Service Charge Exclusions" \l 2

1. Costs arising from any damage or destruction to the Building and/or the Podium caused by an Insured Risk or an Uninsured Risk.

2. Capital costs of the construction, alteration, redevelopment or extension of the Building or the Podium.

3. Costs of any unlet Lettable Unit.

4. Rent collection costs.

5. Costs incurred in dealing with any lettings or rent reviews at the Building.

6. Unrecovered costs due from another tenant of the Building.

7. Costs incurred in dealing with the Landlord's interest in the Building or the Podium, including the costs of advertising and promotional or publicity activities relating to any proposed dealing with the Landlord's interest in the Building or the Podium.

8. Any expenditure in respect of which the Landlord has recovered the cost from any third party by way of warranty claims or claims under guarantees provided the cost of recovering such sums shall be a Service Cost where such sums were not recovered from such third party and the Landlord is to use all reasonable and commercially sensible endeavours to recover such expenditure and cost from such a third party.

4 SCHEDULE 4

Insurance and Damage Provisions TC "4 Insurance and Damage Provisions" \l 3

1. **Tenant's insurance obligations**

1.1 The Tenant must pay on demand:

1.1.1 a fair and reasonable proportion of:

(a) the sums the Landlord pays to comply with **paragraphs 2.1.1 and 2.1.2**;

(b) if not recovered through the service charge, the sums the Landlord pays to insure all plant, machinery, apparatus and vehicles used in providing the Services;

(c) the cost of valuations of the Podium, the Building and the Premises for insurance purposes made not more than once a year; and

(d) the amount of any excess or deductible under any insurance policy that the Landlord incurs or will incur in complying with **paragraphs 2.3 and 2.4**;

1.1.2 the whole of the sums the Landlord pays for insuring loss of the Main Rent and Service Charge for the Risk Period;

1.1.3 a sum equal to the amount that the insurers refuse to pay following damage or destruction by an Insured Risk to the Podium and/or the Building because of the Tenant's act or failure to act; and

1.1.4 any additional or increased premiums that the insurers may require as a result of the carrying out or retention of any Permitted Works or the Tenant's or any lawful occupier's use of the Premises.

1.2 The Tenant must comply with the requirements of the insurers and must not do anything that may invalidate any insurance.

1.3 The Tenant must not use the Premises for any purpose or carry out or retain any Permitted Works that may make any additional premium payable for the insurance of the Premises or the Building or the Podium, unless it has first agreed to pay the whole of that additional premium.

1.4 The Tenant must notify the Landlord as soon as practicable after it becomes aware of any damage to or destruction of the Premises by any of the Insured Risks or by an Uninsured Risk.

1.5 The Tenant must keep insured, in a sufficient sum and with a reputable insurer, public liability risks relating to the Premises.

2. **Landlord's insurance obligations**

2.1 The Landlord must insure (with a reputable insurer):

2.1.1 the Building and the Podium against the Insured Risks in its full reinstatement cost (including all professional fees and incidental expenses, debris removal, site clearance and irrecoverable VAT);

2.1.2 against public liability relating to the Building and the Podium; and

2.1.3 loss of the Main Rent and Service Charge for the Risk Period,

subject to all excesses, limitations and exclusions as the insurers may impose and otherwise on the insurer's usual terms.

2.2 In relation to the insurance, the Landlord must:

2.2.1 procure the Tenant's interest in the Premises is noted either specifically or generally on the policy;

2.2.2 take reasonable steps to procure that the insurers waive any rights of subrogation they might have against the Tenant (either specifically or generally); and

2.2.3 provide the Tenant with a summary of its main terms upon the Tenant's written request.

2.3 The Landlord must take reasonable steps to obtain any consents necessary for the reinstatement of the Building and/or the Podium (as may be applicable) following destruction or damage by an Insured Risk.

2.4 Following obtaining the consents referred to above (and when it is lawful to do so), the Landlord must reinstate (as may be applicable) the Building and/or the Podium following destruction or damage by an Insured Risk. Reinstatement need not be identical if the replacement is similar in size, quality and layout.

2.5 If the Landlord is obliged to reinstate the Premises, the Landlord is (if the Building or the Premises is substantially damaged or destroyed) to use all reasonable endeavours to obtain deeds of warranty from the building contractor and all members of the professional team engaged in respect of the design and construction of the reinstate Premises. The warranties must be in favour of the Tenant and in such form as the Tenant approves, such approval not to be unreasonably withheld or delayed.

2.6 Nothing in this **paragraph 2** imposes any obligation on the Landlord to insure or to reinstate tenant's fixtures forming part of the Premises or the Building.

2.7 Nothing in **paragraph 2.4** will require the Landlord to reinstate any Lettable Units other than the Premises.

2.8 The Landlord's obligations under **paragraphs 2.3 and 2.4** will not apply:

2.8.1 unless and until the Tenant has paid the amounts referred to in **paragraph 1.1.1(d)** and, where applicable, **paragraph 1.1.3**; or

2.8.2 if the Landlord notifies the Tenant under **paragraph 4.1** that it ends the Lease.

2.9 If there is destruction or damage to the Building by an Uninsured Risk that leaves the whole or substantially the whole of the Premises unfit for occupation and use or inaccessible and the Landlord notifies the Tenant within six months afterwards that the Landlord wishes to reinstate, **paragraphs 2.3 and 2.4** will then apply as if the damage or destruction had been caused by an Insured Risk.

2.10 Subject to the insurance premiums being reasonable and proper and reasonably and properly incurred, the Landlord will be entitled to retain all insurance commissions for its own benefit.

3. **Rent suspension**

3.1 **Paragraph 3.2** will apply if the Building is destroyed or damaged by any Insured Risk or Uninsured Risk so that the Premises are unfit for occupation or use or inaccessible. **Paragraph 3.2** will not apply to the extent that the Landlord's insurance has been vitiated or payment of any policy moneys refused because of anything the Tenant does or fails to do and the Tenant has not complied with **paragraph 1.1.3**.

3.2 Subject to **paragraph 3.1**, the Main Rent, Service Charge and Parking Space Rent or a fair proportion of them, will not be payable from and including the date of damage or destruction until the earliest of:

3.2.1 the date that the Premises are again fit for occupation and use, accessible and ready to receive the Tenant's fitting out works;

3.2.2 the end of the Risk Period; and

3.2.3 the End Date.

3.3 If **paragraph 3.2** applies before the Rent Commencement Date or during the rent free period referred to in **clause 3.4**, the number of days between the date of damage or destruction and either the Rent Commencement Date or the date on which 100% of the Main Rent again becomes payable (or where only a proportion of the Main Rent is or would have been suspended, an equivalent proportion of those days) will be added to the date the rent suspension ends and the resulting date will become the Rent Commencement Date or the date on which 100% of the Main Rent again becomes payable.

3.4 If **paragraph 3.2** applies:

3.4.1 the Landlord must refund to the Tenant as soon as reasonably practicable a due proportion of any Main Rent and Service Charge paid in advance that relates to any period on or after the date of damage or destruction; and

3.4.2 the Tenant must pay to the Landlord on demand the Main Rent and Service Charge for the period starting on the date they again become payable to but excluding the next Rent Day.

3.5 Any dispute about the application of this **paragraph 3** will be decided at the request of either party by a single arbitrator under the 1996 Act.

4. **Termination**

4.1 **Paragraph 4.3** will apply if there is destruction or damage to the Building by an Insured Risk that leaves the whole or substantially the whole of the Premises unfit for occupation and use or inaccessible and, when the Risk Period ends, the Building has not been reinstated sufficiently so that the Premises are again fit for occupation and use and accessible and ready to receive tenant's fitting out works.

4.2 If there is destruction or damage to the Building by an Uninsured Risk that leaves the whole or substantially the whole of the Premises unfit for occupation and use or inaccessible:

4.2.1 if the Landlord does not notify the Tenant within 12 months after the damage or destruction that the Landlord wishes to reinstate, this Lease will end on the last day of that 12 month period;

4.2.2 if the Landlord notifies the Tenant that the Landlord does not wish to reinstate, this Lease will end on the date of that notification by the Landlord;

4.2.3 **paragraph 4.3** will apply if the Landlord notifies the Tenant that the Landlord wishes to reinstate and, when the Risk Period ends, the Building has not been reinstated sufficiently so that the Premises are again fit for occupation and use and accessible.

4.3 In the circumstances set out in **paragraph 4.1** or **paragraph 4.2.3**, either the Landlord or the Tenant may end this Lease immediately by notifying the other at any time after the end of the Risk Period but before the Premises are again fit for occupation and use and accessible. Unless the damage or destruction was caused by an Uninsured Risk, the exercise of this right by the Tenant is subject to the Tenant complying with **paragraph 1.1.1(d)** and, where applicable, **paragraph 1.1.3**.

4.4 For the purposes of **paragraphs 3.2.2 and 4.2.3**, if the damage or destruction is caused by an Uninsured Risk, the Risk Period will be treated as beginning on the date the Landlord notifies the Tenant of its wish to reinstate under **paragraph 2.9**.

4.5 If this Lease ends under this **paragraph 4**:

4.5.1 that will not affect the rights of any party for any prior breaches;

4.5.2 the Tenant must give vacant possession of the Premises to the Landlord; and

4.5.3 the Landlord will be entitled to retain all insurance moneys.

5 SCHEDULE 5

Works TC "5 Works" \l 3

1. **Defined terms**

This **Schedule 5** uses the following definitions:

"CDM Regulations"

the Construction (Design and Management) Regulations 2015.

"Consents"

all necessary permissions, licences and approvals for the Permitted Works under the Planning Acts, the building and fire regulations, and any other statute, bye law or regulation of any competent authority and under any covenants or provisions affecting the Premises or the Building and as otherwise required from owners, tenants or occupiers of any part of the Building or any adjoining premises.

"Requirements"

the following requirements:

(a) the Tenant will enter into a JCT or a FIDIC construction agreement in respect of the Permitted Works prior to commencing the Permitted Works;

(b) the Tenant shall ensure that:

(i) the on-floor M&E installations are isolated from the rest of the Building while the Permitted Works are undertaken;

(ii) its contractors carry out their own validation of the Permitted Works prior to commencing the Permitted Works;

(iii) the Permitted Works do not cause an overload of the electrical services, take a disproportionate amount of common supplies or adversely impact the systems within the Building; and

(iv) its contractors maintain the water quality in all systems in the course of undertaking the Permitted Works;

(c) the Tenant shall keep the Landlord's building surveyor and the Landlord's M&E consultant informed about the progress of the Permitted Works and shall ensure that the Landlord's building surveyor and the Landlord's M&E consultant are permitted to monitor:

(i) the manner in which the Permitted Works are carried out; and

(ii) (having been given not less than 5 Business Days' prior notice) the commissioning and sign-off of the Permitted Works,

to ensure that the Permitted Works are completed in the manner and form in which they were first approved and to ensure that the Building continues to work efficiently and in line with its design parameters;

(d) prior to the commissioning and signing-off of the Permitted Works the Tenant shall provide the Landlord with:

(i) plans of the Permitted Works overlaid on the plans of the Building's management systems; and

(ii) details of any changes to the operations and maintenance manuals arising from the Permitted Works;

(e) the number and frequency of the inspections referred to in **paragraph (c)** above will depend on the nature of the Permitted Works but, in any event, the Tenant is to ensure that these take place before any closing-up works are undertaken so as to ensure that any hidden services are (as applicable) installed or altered in the manner in which they were first approved;

(f) the Tenant shall only be permitted to connect the on-floor M&E installations to the rest of the Building once the Landlord's building surveyor and the Landlord's M&E consultant have confirmed that the commissioning of such systems have been undertaken in accordance with best practice; and

(g) the Tenant shall pay (within 10 Business Days of demand):

(i) the reasonable and proper costs incurred by the Landlord of employing the Landlord's building surveyor and the Landlord's M&E consultant in the manner referred to within these Requirements; and

(ii) the Landlord's reasonable and proper costs associated with overlaying the plans and specifications of the Permitted Works onto the Building's management system.

2. **Tenant's obligations in relation to Permitted Works**

2.1 Before starting any Permitted Works the Tenant must:

2.1.1 obtain and provide the Landlord with copies of any Consents that are required before they are begun;

2.1.2 fulfil any conditions in the Consents required to be fulfilled before they are begun;

2.1.3 comply with its obligations in **clause 4.21.4**;

2.1.4 notify the Landlord of the date on which the Tenant intends to start the Permitted Works;

2.1.5 provide the Landlord with any information relating to the Permitted Works as may be required by its insurers and, where the policy requires, not begin the Permitted Works until the Landlord notifies the Tenant that the insurers have given their consent to the Permitted Works; and

2.1.6 ensure that it or its building contractor has put in place public liability and employers' liability insurance of at least £10 million in respect of each claim and provided the Landlord with a summary of the main terms of the insurance and evidence that the premiums have been paid.

2.2 If it starts any Permitted Works, the Tenant must carry out and complete them:

2.2.1 diligently and without interruption, and in any event within 12 months of starting the Permitted Works or, if any delay occurs that is outside the reasonable control of the Tenant, within such longer period as may be reasonable having regard to the reason for the delay;

2.2.2 in accordance with any drawings, specifications and other documents relating to the Permitted Works that the Landlord has approved;

2.2.3 in a good and workmanlike manner and with good quality materials;

2.2.4 in accordance with:

(a) the Requirements; and

(b) the reasonable principles, standards and guidelines set out in any relevant guide or handbook published by the Landlord (the Landlord to provide a copy to the Tenant

as soon as reasonably possible following request) from time to time for tenant's works carried out at the Building;

2.2.5 in compliance with the Consents and all Acts (including the Planning Acts) and with the requirements of the insurers of the Building and the Premises and (where applicable) of any competent authority or utility provider;

2.2.6 with as little interference as reasonably practicable to the owners and occupiers of any other parts of the Building or any adjoining premises; and

2.2.7 in compliance, to the extent applicable, with the CDM Regulations.

2.3 The Tenant must make good immediately any physical damage caused by carrying out the Permitted Works.

2.4 The Tenant must permit the Landlord on reasonable notice to enter the Premises to inspect the progress of the Permitted Works.

2.5 Until the Permitted Works have been completed, the Tenant must insure them for their full reinstatement cost (including professional fees) against loss or damage by the Insured Risks with a reputable insurer and provide the Landlord with a summary of the main terms of the insurance.

2.6 The Tenant must reinstate any of the Permitted Works that are damaged or destroyed before their completion.

2.7 Where the Landlord has given the Landlord's consent to any Permitted Works:

2.7.1 the Tenant must comply with any additional obligations in relation to those Permitted Works that the Landlord lawfully imposes on the Tenant in giving the Landlord's consent; and

2.7.2 if the Tenant has not started the Permitted Works within three months after the date of the consent, the Landlord may serve notice on the Tenant to withdraw the consent.

2.8 As soon as reasonably practicable following completion of the Permitted Works the Tenant must:

2.8.1 notify the Landlord of their completion;

2.8.2 obtain any Consents that are required on their completion;

2.8.3 remove all debris and equipment used in carrying out the Permitted Works;

2.8.4 notify the Landlord of the cost of the Permitted Works;

2.8.5 permit the Landlord to enter the Premises to inspect the completed Permitted Works;

2.8.6 supply the Landlord with two complete sets of as-built plans showing the Permitted Works; and

2.8.7 ensure that the Landlord is able to use and reproduce the as-built plans for any lawful purpose.

2.9 If the CDM Regulations apply to the Permitted Works, the Tenant must:

2.9.1 comply with them and ensure that any person involved in the management, design and construction of the Permitted Works complies with their respective obligations under the CDM Regulations;

2.9.2 if the Landlord would be treated as a client for the purposes of the CDM Regulations, agree to be treated as the only client in respect of the Permitted Works; and

2.9.3 on completion of the Permitted Works provide the Landlord with a copy of any health and safety file relating to the Permitted Works and deliver the original file to the Landlord at the End Date.

2.10 If the Permitted Works invalidate or materially adversely affect an existing EPC or require the commissioning of an EPC, the Tenant must (at the Landlord's option):

2.10.1 obtain an EPC from an assessor approved by the Landlord and give the Landlord written details of the unique reference number for that EPC; or

2.10.2 pay the Landlord's costs of obtaining an EPC.

2.11 If any Consents for the Permitted Works require any works to be carried out by a date that falls after the End Date, the Tenant must, if notified by the Landlord at least three months before the End Date, carry out and complete those works before the End Date.

3. **No warranty relating to Permitted Works**

The Landlord gives no express or implied warranty (and the Tenant acknowledges that the Tenant must satisfy itself):

3.1 as to the suitability, safety, adequacy or quality of the design or method of construction of any Permitted Works;

3.2 that any Permitted Works may lawfully be carried out;

3.3 that the structure or fabric of the Premises or the Building is able to accommodate any Permitted Works; or

3.4 that any of the services supplying the Premises or the Building will either have sufficient capacity for or otherwise not be adversely affected by any Permitted Works.

6 SCHEDULE 6

Underletting TC "6 Underletting" \l 3

1. **Defined terms**

This **Schedule 6** uses the following definitions:

"Approved Underlease"

an underlease approved by the Landlord and, subject to any variations agreed by the Landlord in its absolute discretion:

(a) lawfully excluded from the security of tenure provisions of the 1954 Act;

(b) granted without any premium being received by the Tenant;

(c) reserving a market rent, taking into account the terms of the underletting;

(d) containing provisions for rent review at five yearly intervals and otherwise on the same terms as in **Schedule 2**;

(e) containing provisions for change of use and alterations corresponding to those in this Lease;

(f) prohibiting the assignment of part only of the Underlet Premises;

(g) allowing assignment of the whole of the Underlet Premises with the prior consent of the Landlord on terms corresponding to those in this Lease;

(h) containing a covenant by the Undertenant not to create any sub-underlease of the whole or any part of the Underlet Premises;

(i) containing provisions requiring the Undertenant to pay as additional rent the whole or, in the case of an Underlease of a Permitted Part, a due proportion, of the Insurance Rent, Service Charge and other sums, excluding the Main Rent, payable by the Tenant under this Lease; and

(j) containing other provisions corresponding with those in this Lease;

"Approved Undertenant"

a person approved by the Landlord and who has entered into a direct deed with the Landlord agreeing to:

(a) comply with the terms of the Approved Underlease; and

(b) procure that any proposed assignee of the Underlet Premises enters into a direct deed in the same terms as set out in this definition of Approved Undertenant;

"Permitted Part"

any part of the Premises having independent means of access, for general access and for servicing, from the public highway, from the Common Parts or from those parts of the Premises approved by the Landlord as common parts for the use and enjoyment of the Tenant and any permitted undertenants of the Premises;

"Underlease"

the underlease granted following the approval of the Approved Underlease;

"Underlet Premises"

the premises let by an Underlease; and

"Undertenant"

the Approved Undertenant to whom the Tenant grants an Underlease.

2. **Right to underlet**

2.1 Subject to **paragraph** 2.2, the Tenant may, with the Landlord's consent, underlet the whole of the Premises or the whole of a Permitted Part by an Approved Underlease to an Approved Undertenant.

2.2 The Tenant must not allow more than three people (including the Tenant) to have a legal right to occupy the Premises. Any Group Company of the Tenant will count as the Tenant for the purposes of this paragraph.

3. **Obligations in relation to underleases**

3.1 The Tenant must not waive any material breach by an Undertenant of any terms of its Underlease.

3.2 The Tenant must not reduce, defer, accelerate or commute any rent payable under any Underlease.

3.3 On any review of the rent payable under any Underlease, the Tenant must:

3.3.1 review the rent of the Underlease in compliance with its terms;

3.3.2 not agree the reviewed rent (or the appointment of any third party to decide it) without the Landlord's approval;

3.3.3 include in the Tenant's representations to any third party any representations that the Landlord may require; and

3.3.4 notify the Landlord what the reviewed rent is within two weeks of its agreement or resolution by a third party.

3.4 The Tenant must not:

3.4.1 vary the terms; or

3.4.2 accept any surrender of the whole,

of any Underlease without the Landlord's approval.

3.5 The Tenant must not accept the surrender of any part (rather than the whole) of the Underlet Premises.

Executed as a deed by)
245 HAMMERSMITH ROAD NOMINEE 1)
LIMITED acting by a director in the)
presence of:)

Signature of director

Witness Signature:

Witness Name:

Witness Address:

Executed as a deed by)
245 HAMMERSMITH ROAD NOMINEE 2)
LIMITED acting by a director in the)
presence of:)

Signature of director

Witness Signature:

Witness Name:

Witness Address:

Executed as a deed by)
245 HAMMERSMITH ROAD LIMITED) **PARTNERSHIP** acting by **245**)
HAMMERSMITH ROAD GENERAL)
PARTNER LIMITED as general partner,)
acting by)
in the presence of:)

Signature of director

Witness Signature:

Witness Name:

Witness Address:

Signed as a deed by **ORCHARD**)
THERAPEUTICS (EUROPE) LIMITED)
acting by a director in the presence of)

Director

Witness Signature:

Witness Name:

Witness Address:

Exhibit 31.1

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

I, Bobby Gaspar, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Orchard Therapeutics plc;

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

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

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

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

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

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

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

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

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

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

Date: August 4, 2022

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

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

I, Frank E. Thomas, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Orchard Therapeutics plc;

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

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

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

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

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

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

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

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

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

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

Date: August 4, 2022

By: /s/ Frank E. Thomas
Frank E. Thomas
President and Chief Operating Officer
(Principal Financial Officer and Principal Accounting Officer)

Exhibit 32.1

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

In connection with the Quarterly Report of Orchard Therapeutics plc (the "Company") on Form 10-Q for the period ending June 30, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers does hereby certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

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

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

Date: August 4, 2022 By: /s/ Bobby Gaspar
Bobby Gaspar
Chief Executive Officer
(Principal Executive Officer)

Date: August 4, 2022 By: /s/ Frank E. Thomas
Frank E. Thomas
President and Chief Operating Officer
(Principal Financial Officer and Principal Accounting Officer)