UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 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: 001-38520

MEIRAGTX HOLDINGS PLC

(Exact name of registrant as specified in its charter)

Cayman Islands (State or other jurisdiction of incorporation or organization)	**98-1448305** (I.R.S. Employer Identification No.)
450 East 29th Street, 14th Floor **New York, NY** (Address of principal executive offices)	**10016** (Zip Code)

(646) 860-7985
(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol(s)	Name of exchange on which registered
Ordinary Shares, $0.00003881 par value per share	**MGTX**	**The Nasdaq Global Select Market**

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

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes ☐ No ☒

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

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

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

Large accelerated filer	☐	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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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 June 30, 2022, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's ordinary shares held by non-affiliates of the registrant was approximately $242,659,643 (based upon the closing sale price of the registrant's ordinary shares on that date on the Nasdaq Global Select Market).

As of March 8, 2023, the registrant had 48,666,263 ordinary shares outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement relating to its 2023 annual shareholder meeting to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2022 are incorporated herein by reference in Part III of this Annual Report on Form 10-K.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K (the "Form 10-K") contains forward-looking statements that can involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this Form 10-K, including statements regarding our future results of operations and financial position, business strategy, financing arrangements, prospective products, product approvals, research and development costs, future revenue, timing and likelihood of success, plans and objectives of management for future operations, future results of anticipated products and prospects, plans and objectives of management are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential," "would" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this Form 10-K are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Form 10-K and are subject to a number of risks, uncertainties and assumptions described under the sections in this Form 10-K entitled "Item 1A. Risk Factors" and "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this Form 10-K. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Thus, one should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

You should read this Form 10-K and the documents that we reference in this Form 10-K and have filed as exhibits to this Form 10-K, completely and with the understanding that our actual future results may be materially different from what we expect.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this Form 10-K, 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 relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements. These statements should not be relied upon as representing our views as of any date subsequent to the date of this Form 10-K.

RISK FACTOR SUMMARY

We are providing the following summary of the principal risk factors contained in this Form 10-K to enhance the readability and accessibility of our risk factor disclosures. We encourage you to carefully review in their entirety the full risk factors set forth in the section of this Form 10-K captioned "Item 1A. Risk Factors" for additional information regarding the material factors that make an investment in our ordinary shares speculative or risky. These risks and uncertainties include, among others, the following:

- We have incurred significant losses since inception and anticipate that we will incur continued losses for the foreseeable future, and may never achieve or maintain profitability.
- We will require additional capital to fund our operations, which may not be available on acceptable terms, if at all.
- We may not have sufficient cash flows or cash on hand to satisfy our debt obligations or covenants under our financing arrangements, or we may not be able to effectively manage our business in compliance with such covenants.
- We are heavily dependent on the success of our Most Advanced Product Candidates (as defined in "Item 1A. Risk Factors"), which are still in development, and if none of them receive regulatory approval or are successfully commercialized, our business may be harmed.
- COVID-19 has impacted and may continue to impact our business, and any other pandemic, epidemic or outbreak of an infectious disease may materially and adversely impact our business, including our preclinical studies, clinical trials, manufacturing capabilities and regulatory approvals.
- It is difficult to predict the time and cost of product candidate development on our novel gene therapy platform. Very few gene therapies have been approved in the United States or in Europe.
- Because gene therapy is novel and the regulatory landscape that governs any product candidates we may develop is uncertain and may change, we cannot predict the time and cost of obtaining regulatory approval, if we receive it at all, for any product candidates we may develop.
- Clinical trials are expensive, time-consuming, difficult to design and implement, and involve an uncertain outcome. Further, we may encounter substantial delays in our clinical trials.
- The affected populations for our product candidates may be smaller than we or third parties currently project, which may affect the addressable markets for our product candidates.
- We and our contract manufacturers for plasmid are subject to significant regulation with respect to manufacturing our products. Our manufacturing facilities and the third-party manufacturing facilities which we rely on may not continue to meet regulatory requirements and have limited capacity.
- Enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may affect the prices we may set.
- We are subject to government regulation and other legal obligations relating to privacy and data protection. Compliance with these requirements is complex and costly. Failure to comply could materially harm our business.

- We face significant competition in an environment of rapid technological change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer or more advanced or effective than ours, which may harm our financial condition and our ability to successfully market or commercialize any product candidates we may develop.

- We depend on proprietary technology licensed from others. If we lose our existing licenses or are unable to acquire or license additional proprietary rights from third parties, we may not be able to continue developing our product candidates.

- If we are unable to obtain and maintain patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

- We may need to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

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

BASIS OF PRESENTATION

Unless the context otherwise requires, references in this Form 10-K to "Meira," "MeiraGTx," "we," "us", "our" or "the Company" refer to MeiraGTx Holdings plc and its subsidiaries.

We have proprietary rights to trademarks, trade names and service marks appearing in this Form 10-K that are important to our business. Solely for convenience, the trademarks, trade names and service marks may appear in this Form 10-K without the ® and TM symbols, but any such references are not intended to indicate, in any way, that we forgo or will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensors to these trademarks, trade names and service marks. All trademarks, trade names and service marks appearing in this Form 10-K are the property of their respective owners.

INDUSTRY AND OTHER DATA

We obtained the industry, market and competitive position data in this Form 10-K from our own internal estimates and research as well as from industry and general publications and research, surveys and studies conducted by third parties. Industry publications, studies and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified market and industry data from third-party sources. While we believe our internal company research as to such matters is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.

PART I

ITEM 1. BUSINESS

Overview

We are a vertically integrated, clinical stage gene therapy company with six programs in clinical development and a broad pipeline of preclinical and research programs. We have core capabilities in viral vector design and optimization and gene therapy manufacturing, as well as a potentially transformative gene regulation platform technology that allows precise, dose responsive control of gene expression by oral small molecules with dynamic range that can exceed 5000-fold. Led by an experienced management team, we have taken a portfolio approach by licensing, acquiring and developing technologies that give us depth across both product candidates and indications. The Company's initial focus is on three distinct areas of unmet medical need: ocular diseases, including both inherited retinal diseases as well as large degenerative ocular diseases, neurodegenerative diseases and severe forms of xerostomia. Though initially focusing on the eye, central nervous system and salivary gland, we intend to expand our focus in the future to develop additional gene therapy treatments for patients suffering from a range of serious diseases.

We own and operate a flexible and scalable viral vector manufacturing facility in London, United Kingdom that we expect can supply our current ophthalmology, neurodegenerative disease and salivary gland clinical and preclinical programs through regulatory approval and, should they be approved, provide sufficient capacity for commercial production. Completed in early 2018 and designed to meet global regulatory requirements, including the current good manufacturing practices, or cGMP, required by the U.S. Food and Drug Administration, or FDA, our 29,000 square foot facility has two cell production suites, three independent viral vector production suites providing multi-product and multi-viral vector manufacturing capabilities and an integrated, flexible fill-and-finish suite. In May 2018, we were granted a license to manufacture gene therapy product candidates in our cGMP compliant manufacturing facility by the United Kingdom's Medicines and Healthcare products Regulatory Agency, or MHRA. The MHRA re-certified the facility in the second quarter of 2020.

We have expanded our manufacturing capabilities with our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland. Coming online in 2022 and stretching over 150,000 square feet, it is the first commercial-scale gene therapy manufacturing site in Ireland and is unique in its scale and integrated capabilities. The site contains three facilities, one built to be flexible and scalable for viral vector production for clinical and commercial supply, in addition, a facility to manufacture plasmid DNA – the critical starting material for producing gene therapy products – and thirdly, a Quality Control (QC) hub performing advanced biochemical quality control testing for MeiraGTx clinical and commercial programs. We completed the acquisition of the facilities in January 2021. We believe the completion of our second viral vector manufacturing facility and bringing cGMP plasmid and DNA production in-house will provide greater flexibility and efficiency as we advance our product candidates through development, and should they be approved, commercial production.

We have also established a comprehensive platform for the efficient clinical development of the next generation of gene therapies and manufacturing in accordance with cGMP. Our deep understanding of disease models informs our development of potency assays for the cGMP production of our product candidates, and our teams experienced in viral vector design and optimization work closely with our process development team to design viral vectors and develop proprietary production cell lines for efficient scaling of manufacturing processes. Our wholly-owned facilities have now produced GMP clinical trial material for six different indications, using multiple AAV serotypes, including administration into the eye, salivary gland and central nervous system.

We are also developing a potentially transformative technology to precisely and specifically control gene therapy expression levels via dose-response to orally delivered small molecules. The aim of this gene regulation platform technology is to transform gene therapy into a generalizable delivery mechanism for biologic drugs using a

small molecule “switch” for temporal control. We believe the capacity for temporal control of gene therapy products has the potential to transform the gene therapy landscape by opening up new treatment possibilities.

Our Pipeline

Our initial focus is on three distinct areas of unmet medical need: ocular diseases, including inherited retinal diseases, or IRDs, as well as large degenerative ocular diseases, severe forms of xerostomia and neurodegenerative diseases. Utilizing our product development platform, we have assembled a pipeline of gene therapies to treat these serious diseases. Our criteria for selecting our initial product candidates included:

- unmet medical need;
- high potential for meaningful clinical benefit;
- promising preclinical data using multiple animal models as well as human stem cell derived organoids;
- compartmentalized anatomy of target tissue and the partially immune protected nature of target tissue; and
- understanding of the disease state from natural history studies and detailed long-term characterization of patients prior to entry into gene therapy treatment studies.

A summary of our product candidates and the status of such product candidates as of March 1, 2023 is described below. We retain worldwide development and commercialization rights to all of our product candidates, with the exception of AAV-CNGB3, AAV-CNGA3 and botaretigene sparoparvovec, formerly referred to as AAV-RPGR, which are subject to a strategic Collaboration, Option and License Agreement (the “Collaboration Agreement”) that we executed with Janssen Pharmaceuticals, Inc. (“Janssen”), one of the Janssen Pharmaceutical Companies of Johnson & Johnson, on January 30, 2019.

Product	Indication	Discovery / Preclinical	Phase 1/2	Phase 3
Ocular				
Inherited Retinal Diseases				
Botaretigene sparoparvovec*[1] (janssen)	X-linked RP	PRIME, Fast Track, Orphan Drug		lumeos XLRP study
AAV-RPE65	RPE65-Associated Retinal Dystrophy	RPDD, Orphan Drug		
AAV-CNGB3* (janssen)	Achromatopsia	RPDD, PRIME, Fast Track, Orphan Drug		
AAV-CNGA3* (janssen)	Achromatopsia	RPDD, Fast Track, Orphan Drug		
AAV-AIPL1	LCA4	Compassionate use under MHRA Specials License		
A007, A008,	Undisclosed IRD Targets			
Degenerative Ocular Diseases (non-inherited)				
A006	Wet AMD (anti-VEGFR2)			
Neurodegenerative Disease				
AAV-GAD	Parkinson’s Disease			
AAV-UPF1	ALS			
Salivary Gland				
AAV-AQP1	Xerostomia	Orphan Drug		
	Sjögren’s Syndrome			
Other Pre-IND Programs				
Inherited Obesity (MC4R) / Neurodegenerative disease	AAV-BDNF			
Wilson Disease	AAV-ATP7B opti			
Small molecule riboswitch inducers				

In addition to these clinical and preclinical programs, we have preclinical and research programs in other indications and novel molecular technologies that we aim to advance into clinical development, including:

- gene regulation—use of our proprietary RNA shape regulation cassette to switch gene therapy expression on and off with small molecules, potentially transforming gene therapy technology into a delivery mechanism for a broad array of biologic drugs;

- geographic atrophy age related macular degeneration, or dry AMD—use of gene therapy technology to introduce light sensitive molecules into rod photoreceptors in order to restore some aspects of vision lost in this disease;

- other ocular conditions—glaucoma and uveitis;

- Alzheimer's disease—targeting endosomal trafficking, which is a central mechanism that we believe underlies Alzheimer's disease;

- central nervous systems/peripheral nervous system diseases—brain-derived neurotrophic factor gene therapy for treatment of genetic obesity disorders, as well as the development of gene therapy product candidates for other central nervous system diseases; and

- inflammatory/autoimmune diseases—use of gene therapy technology for the local delivery of immunomodulatory therapeutics, including osteoarthritis, gout and certain rare inflammatory disorders.

Our Ophthalmology Programs

Eye diseases are our first area of clinical focus and we aim to provide treatments with durable, long-term clinical benefit that will halt vision loss in patients. We are actively dosing patients in our Phase 3 Lumeos clinical trial for botaretigene sparoparvovec for the treatment of X-linked retinitis pigmentosa related to mutations in the *RPGR* gene, or XLRP-RPGR. We also have three Phase 1/2 clinical programs targeting IRDs, including AAV-CNGB3 and AAV-CNGA3 for the treatment of achromatopsia, or ACHM, related to mutations in *CNGB3* and *CNGA3* genes, respectively, and AAV-RPE65 for retinal dystrophy related to mutations in the *RPE65* gene, or RPE65 deficiency. We have completed enrollment and dosing in all three of these programs. In addition to these four programs, AAV-AIPL1 has been manufactured and released for compassionate use under an MHRA specials license in the United Kingdom, or UK, to treat patients with Leber congenital amaurosis 4, or LCA4, caused by mutations in the *AIPL1* gene. In addition to these clinical programs in IRDs, we have preclinical programs that apply novel approaches to both wet and dry AMD, glaucoma and uveitis, as well as several other IRDs including retinol dehydrogenase 12, or RDH12, mutation-associated retinal dystrophy.

We chose diseases of the eye as our first area of clinical focus because we believe the eye is ideally suited for gene therapy for the following reasons.

- The eye is easily accessible and has highly compartmentalized anatomy, which allows for accurate delivery of vectors to specific tissues using direct visualization and microsurgical techniques.

- The structure of the eye allows for efficient delivery to specific cell subtypes with small volumes of vector, making the dose per patient much lower than is needed for systemic treatment.

- Anatomical barriers and unique structure of the eye make the immune response to the intraocular administration of vectors more attenuated than systemic administration.

- Largely non-dividing cell populations in the eye make good targets for potentially stable, long-term gene delivery and expression.

- The retina, a structure in the back of the eye, is visible and there are many well validated structural and functional readouts allowing the detailed assessment of the therapeutic impact of the gene therapy treatment.

Our strategy for developing gene therapies targeting eye diseases is to begin with a number of monogenic IRDs that are good candidates for gene replacement therapies and expand to more common eye diseases over time. We have taken a portfolio approach to the development of IRDs because, while some of these genetic defects are rare, IRDs as a class are one of the most common causes of blindness in working age adults and there are multiple synergies at the clinical, regulatory and commercial levels between many of these diseases caused by different gene mutations.

The deep scientific and clinical understanding of IRDs driving our approach to gene therapy development helps us to optimize our product candidates for each specific genetic mutation and phenotype. We develop our viral vectors by selecting and modifying proprietary cell specific promoters, selecting appropriate capsids for transfection of target cells and refining the vector for efficient production and scalable manufacturing. Not only does this allow us to synergistically target a portfolio of inherited eye conditions, we also believe it has potential to be applied to the development of gene therapies for other diseases.

Our longstanding relationships with leading institutions in retinal disease treatment, including the Moorfields Eye Hospital in London, the University of Michigan Kellogg Eye Center, Massachusetts Eye and Ear, the Medical College of Wisconsin & Froedtert Hospital and the Casey Eye Institute at the Oregon Health & Science University, provide us with access to experts whose guidance and insight informs our development strategy, as well potential patients for our clinical trials.

We intend to leverage our platform to take advantage of the many synergies across our ophthalmology programs, including identification, diagnosis and characterization of patients, specialized surgical techniques, clinical and regulatory process, vector production and cGMP manufacturing.

Botaretigene Sparoparvovec for the Treatment of X-Linked Retinitis Pigmentosa Associated with Mutations in the RPGR Gene

Retinitis pigmentosa, or RP, is a group of IRDs which represent the most common genetic cause of blindness. The condition is characterized by progressive retinal degeneration and vision loss that ends in complete blindness. RP initially presents as nighttime blindness during childhood or early adulthood, progressing to peripheral visual field loss and “tunnel vision,” central visual impairment, reduced visual acuity and, ultimately, complete blindness.

RP may be caused by mutations in any of over 100 different genes. The most severe forms of RP are X-linked, or XLRP, with onset in early childhood and rapid progression to blindness generally by the time patients reach 30 to 40 years old. The most frequent mutation causing XLRP is in the retinitis pigmentosa GTPase regulator gene, or *RPGR*. XLRP associated with a mutation in RPGR, or XLRP-RPGR, accounts for more than 70% of cases of XLRP. There are estimated to be approximately 20,000 XLRP-RPGR patients in the United States (U.S.), Japan and Germany, France, Spain, Italy and the UK, or the EU5, with a little less than 50% of those patients being under the age of 40 and approximately 200 new cases being diagnosed annually. We believe the availability of a therapeutic option may increase patient identification and the estimated prevalence of XLRP-RPGR.

There are currently no approved treatments for XLRP.

Clinical Development of Botaretigene Sparoparvovec

We have an ongoing natural history study in XLRP-RPGR including approximately 100 patients, which allows us to collect structural and functional data for up to five years on prospectively defined endpoints, including functional tests, retinal imaging and electrophysiological assessments. We believe access to this large population of XLRP-RPGR patients has enabled us to efficiently enroll appropriate patients into our XLRP clinical development program.

Since XLRP-RPGR is a progressive disease in which the retina gradually degenerates starting in the outer, or peripheral, regions of the retina and initially causing "tunnel vision" with final degeneration of the central retina resulting in the complete loss of visual acuity and blindness that generally occurs by the time patients are 30 to 40 years old, we believe that the central region of the retina, including the macula and fovea, must be preserved to prevent the ultimate degeneration to blindness and to retain visual acuity. To this end, we aim to deliver botaretigene sparoparvovec to this central region of the retina.

We conducted a Phase 1/2 clinical trial of botaretigene sparoparvovec in XLRP patients. Botaretigene sparoparvovec was delivered via subretinal injection of up to 1mL with the potential for the surgeon to use multiple retinotomies targeting the region of the central retina, including the macula and fovea.

In the dose escalation portion of the Phase 1/2 trial, we enrolled 13 patients, including 10 young adults and 3 children. After we completed dosing patients in the dose escalation portion of the study, we enrolled patients in the randomized, controlled, extension portion of the Phase 1/2 trial. We disclosed six-month data from the dose escalation portion of the study as a late-breaker at the American Society of Retina Specialists 2020 Virtual Annual Meeting in July 2020, nine-month data at EURETINA 2020 Virtual Congress in October 2020 and twelve-month data at the American Academy of Ophthalmology, or AAO, 2020 Virtual Annual Meeting in November 2020. Data from each time point revealed that patients treated with low (n=3) and intermediate (n=4) dose botaretigene sparoparvovec experienced statistically significant improvement in retinal sensitivity. Nine-month data also indicated significant improvement in vision-guided mobility, and at 12-months, six of seven patients continued to show improved or stable vision in the treated eye. Each patient was treated with subretinal delivery of botaretigene sparoparvovec in one eye and the patient's other eye served as an untreated control. The primary endpoint of the trial is safety, with secondary endpoints assessing changes in visual function at pre-specified timepoints post-treatment. Baseline values were determined in triplicate.

We disclosed additional twelve-month clinical data from the dose escalation portion of the Phase 1/2 trial as part of an oral presentation at the EURETINA 2021 Virtual Congress in September 2021. The retinal function of ten adult males aged 18-30 years with RPGR-associated XLRP was assessed twelve months post-treatment. For the intermediate dose-escalation dose cohort (n=4), intervention with botaretigene sparoparvovec in the poorer-seeing eye altered the course of natural disease progression. At twelve months post-intervention, mean retinal sensitivity (MS) and volumetric analysis of the central 30 degrees of the retinal field (V30) in the treated eye were similar to levels observed twenty-four months pre-intervention, while the untreated eye showed a continued downward trajectory.

We also disclosed positive data from the Phase 1/2 clinical trial at the AAO 2022 Annual Meeting in October 2022. Treatment with botaretigene sparoparvovec was found to be generally safe and well-tolerated, with no dose-limiting events. Adverse events profile was anticipated and manageable, with most adverse events related to the surgical delivery procedure, transient and resolved without intervention. A total of three serious adverse events were observed in the overall Phase 1/2 clinical study; two serious adverse events, which were previously reported, were observed in the dose-escalation phase of the study (n=10; one retinal detachment and one panuveitis in the low dose cohort), and a single additional serious adverse event of increased intraocular pressure was observed in the dose escalation phase and resolved with treatment. Sustained or increased functional improvements were demonstrated at six months post-treatment in multiple endpoints across each of the three domains of vision -- retinal function, visual function, and functional vision --

in patients treated with botaretigene sparoparvovec when compared to the randomized untreated control arm of the study.

We are actively dosing patients in our Phase 3 Lumeos clinical trial, a randomized, controlled study of botaretigene sparoparvovec for the treatment of XLRP associated with variants in the *RPGR* gene.

The FDA has granted Fast Track and orphan drug designations to botaretigene sparoparvovec. Competent authorities in the European Union, or EU, have granted Priority Medicines, or PRIME, advanced therapy medicinal product, or ATMP, and orphan drug designations to botaretigene sparoparvovec.

AAV-RPE65 for the Treatment of RPE65-Associated Retinal Dystrophy

We are developing AAV-RPE65 for the treatment of retinal dystrophy associated with mutations in the *RPE65* gene. *RPE65*-associated retinal dystrophy causes rod photoreceptor dysfunction and impaired vision from birth. Absence of RPE65 results in severe dysfunction of rods and causes impaired vision in dim lighting conditions. Although cone photoreceptors are generally preserved during childhood in *RPE65*-deficient patients, the lack of function and degeneration of the rods eventually results in the loss of cones and degeneration of the whole retina over time. Consequently, most *RPE65*-associated retinal dystrophy patients experience central vision loss progressing to complete blindness by early adulthood.

Based on an estimated prevalence of approximately one in 500,000 people in the United States suffering from Leber congenital amaurosis, or LCA, related to mutations in the *RPE65* gene, and approximately one in 70,000 people in the United States having RP due to mutations in the *RPE65* gene, *RPE65*-deficiency occurs in approximately one in 125,000 people in the United States. There are estimated to be approximately 6,000 *RPE65*-deficiency patients in the United States, Japan and EU5, with almost 30% of those patients being under the age of 30 and approximately 50 new cases being diagnosed annually. We have developed a gene therapy candidate optimized for safety and potency for the treatment of *RPE65*-associated retinal dystrophy, AAV-RPE65. AAV-RPE65 is an AAV2/5 viral vector, in which a codon optimized *RPE65* gene is driven by a novel synthetic retinal pigment epithelium cell specific promoter.

The FDA has approved the first gene treatment for *RPE65*-associated retinal dystrophy, Luxturna, a commercially available product developed by Spark Therapeutics, Inc., which was purchased by Roche. While *RPE65*-associated retinal dystrophy primarily causes a loss of rod function initially leading to impaired vision in dim light, these patients ultimately experience complete blindness because of degeneration of the cone rich fovea. To prevent blindness, therefore, we believe it is critical to treat the central retina in order to maintain structural integrity in this region and save central vision. We aim to treat as extensive an area of the central retina as possible, including the cone rich fovea. Thus, in addition to improving rod function, we aim to provide sufficient RPE65 protein to the cells in the central retina to prevent the degeneration of both rods and cones in this region, and thereby prevent the progression to complete blindness.

Clinical Development of AAV-RPE65

We have an ongoing natural history study in patients with RPE65-associated retinal dystrophy with approximately 30 patients enrolled that allows us to collect structural and functional data on prospectively defined endpoints, including functional tests, retinal imaging, and electrophysiological assessments.

Our Phase 1/2 clinical trial enrolled *RPE65*-associated retinal dystrophy patients in the UK and U.S. Dosing in the Phase 1/2 clinical trial was completed in June 2018. The primary endpoint of this open-label, dose-escalation clinical trial is safety. Secondary endpoints include the outcomes of a range of functional tests, detailed structural analysis of the retina and quality of life measures. A total of 15 patients were treated in this clinical trial, including nine adult patients in three dose escalation cohorts and six pediatric patients in the pediatric extension arm of the trial.

In May 2019, we announced positive topline safety and efficacy data from the Phase 1/2 trial of AAV-RPE65. Additional data from this study were presented at the Retina Subspecialty Day of the American Academy of Ophthalmology Annual Meeting in October 2019.

AAV-RPE65 met the study's primary endpoint of safety and tolerability. Additionally, AAV-RPE65 demonstrated statistically significant improvement across several secondary endpoints assessing clinical activity. Significant improvement in vision was demonstrated at six months after AAV-RPE65 treatment, as measured by assessments of vision-guided mobility, retinal sensitivity, visual acuity and contrast sensitivity. Larger improvements from baseline in functional vision were observed between treated and control eyes at lower light levels. We believe these outcomes address the core functional manifestation of *RPE65*-associated retinal dystrophy, which typically causes vision impairment beginning in early childhood that is most pronounced in low-light conditions, and is consistent with the proposed mechanism of action of AAV-RPE65.

We continue to evaluate the initiation of a Phase 3 clinical trial for AAV-RPE65.

The FDA and European Medicines Agency, or EMA, each granted orphan status to AAV-RPE65 for the treatment of LCA caused by mutations in the *RPE65* gene. The FDA also granted AAV-RPE65 rare pediatric disease designation for the treatment of inherited retinal dystrophy due to biallelic *RPE65* mutations.

AAV-CNGB3 and AAV-CNGA3 for the Treatment of Achromatopsia

Achromatopsia, or ACHM, is an IRD that specifically prevents cone photoreceptors from functioning. ACHM patients are legally blind from birth and usually suffer from severely reduced visual acuity of 20/200 or worse, a disabling sensitivity to light, or photoaversion, total color blindness and involuntary back and forth eye movements, or nystagmus. ACHM patients suffer significant vision loss due to the complete lack of cone function. ACHM occurs in approximately one in 30,000 people in the United States. The *CNGB3* and *CNGA3* genes are the two most common genes that have been identified as causing ACHM, together accounting for up to 92% of ACHM cases, with *CNGB3* slightly more common than *CNGA3* in most geographic territories.

There are estimated to be approximately 12,000 patients with ACHM caused by mutations in *CNGB3* in the United States, Japan, and the EU5, with about 25% of those patients being under the age of 18 and approximately 125 new cases being diagnosed annually. We believe the availability of a therapeutic option may increase patient identification and the estimated prevalence of ACHM.

ACHM is predominantly a stationary disease, which means that ACHM patients' retinas contain non-functioning cones that survive intact for many decades. This is in contrast to many IRDs in which the entire retina slowly degenerates over a patient's life. This extended survival of cones with their potential for light sensitivity presents a wide window of opportunity to introduce a normal copy of the mutated gene via a gene therapy product candidate and thereby restore cone function. While the stationary nature of ACHM means that cones remain present for decades, the functional connections between active cones and the visual cortex in the brain are thought to become fixed in teenage years. Therefore, we believe that younger individuals are likely to benefit most from gene therapy treatment for ACHM because of their greater visual plasticity. Another debilitating symptom of ACHM, which lasts throughout life, is photoaversion. A disabling and ubiquitous symptom of ACHM, photoaversion is the avoidance of light due to discomfort in the presence of levels of light equivalent to a normally lit room or daylight. ACHM patients often avoid light and wear dark glasses, which further diminishes their already very poor vision. We believe it is possible that restoration of cone function in adult patients might have an impact on photoaversion even if brain plasticity is limited.

We believe that gene therapy treatment for ACHM in which we aim to restore cone function via a gene replacement strategy may offer benefits across a range of ages, which we aim to define in our clinical development programs.

We have designed specifically optimized gene therapy viral vector candidates to treat ACHM caused by mutations in each of *CNGB3* and *CNGA3*, with which we aim to address the majority of patients suffering from ACHM. Our product candidates are delivered via subretinal injection covering the central macula region of the eye, where most of the cones in the retina are located.

We have an ongoing natural history study in ACHM including over 90 patients that allows us to collect structural and functional data for up to five years on prospectively defined endpoints, including functional tests, retinal imaging and electrophysiological assessments. We believe access to these ACHM patients has enabled us to efficiently enroll the most appropriate patients into our *CNGB3* and *CNGA3* Phase 1/2 clinical trials. In addition to giving us access to patients and potentially accelerated enrollment in our treatment studies, we believe the prospective natural history data on each treated patient allow us to gather robust data from our Phase 1/2 clinical trials in a condensed timeframe.

Clinical Development of AAV-CNGB3 for the Treatment of ACHM Caused by Mutations in the CNGB3 Gene

We have developed a product candidate, AAV-CNGB3, to treat ACHM caused by mutations in the *CNGB3* gene. Mutations in the *CNGB3* gene prevent cone photoreceptors from functioning because *CNGB3*'s gene product is integral to the formation of a specific membrane channel that enables cones' electrical response to light. *CNGB3* is a gene exclusively expressed in cones and our aim is to replace the absent function of the mutant *CNGB3* gene with a normal copy of the gene in cones of IRD patients and thereby restore cone function. In order to drive expression of the functional *CNGB3* gene specifically in cones and not in other cells of the retina, we use the cone specific human cone arrestin, or CAR, promoter to drive the expression of a codon optimized *CNGB3* cDNA. Codon optimization improves protein expression by increasing translation efficiency. To transfect cone photoreceptors, we use the AAV8 capsid, which enables the efficient delivery of the *CNGB3* gene cargo to those photoreceptors. As the vast majority of the cones in the eye are located centrally and concentrated in the macula, we treat this central region of the retina through subretinal injection to deliver the viral vector product candidate to the photoreceptors in which its activity is required.

We have completed enrollment and dosing of the Phase 1/2 clinical trial of AAV-CNGB3 in both adult and pediatric patients. In this trial, AAV-CNGB3 was delivered via subretinal injection of up to 0.5mL targeting the central region of the retina, including the macula and fovea, where most of the cones are located. One eye is treated in each patient. The primary endpoint of this open-label, dose-escalation clinical trial is safety. Secondary endpoints include the outcomes of a range of functional and structural assessments.

Dosing was completed in this clinical trial in May 2019. In the dose escalation portion of the trial, we treated 11 adults. We also treated 12 children in the pediatric expansion cohorts. Six months following treatment, patients can move onto a long term follow up study in which they are followed for safety and indication of benefit for an additional four and a half years.

Our gene therapy product candidate AAV-CNGB3 was granted orphan drug designation by the FDA and the European Commission for the treatment of achromatopsia caused by mutations in the *CNGB3* gene, rare pediatric disease designation by the FDA for the treatment of achromatopsia caused by mutations in the *CNGB3* gene, and Fast Track designation by the FDA for the treatment of achromatopsia caused by *CNGB3* mutations. We were granted PRIME designation by the EMA in October 2018 based on data from the first adult treatment cohort along with preclinical data.

Clinical Development of AAV-CNGA3 for the Treatment of ACHM Caused by Mutations in the CNGA3 Gene

We are also developing AAV-CNGA3 to treat ACHM caused by mutations in the *CNGA3* gene. We have designed a synthetic promoter to drive high levels of *CNGA3* expression specifically in cones because we believe a larger amount of *CNGA3* protein is required to restore cone function as compared to *CNGB3*. AAV-CNGA3 utilizes this proprietary pan cone promoter to drive a codon optimized *CNGA3* gene sequence. We believe this novel promoter can

drive sufficient expression of *CNGA3* in cones to restore light sensitivity to these cones in *CNGA3* deficient patients. We use the AAV8 capsid to transfect cone photoreceptors in the back of the eye and we target the cones concentrated in the central region of the retina via a subretinal injection that covers the macula.

We have completed enrollment and dosing of the open-label, dose-escalation Phase 1/2 clinical trial of AAV-CNGA3 in patients with ACHM due to mutations in the *CNGA3* gene.

Our gene therapy product candidate AAV-CNGA3 was granted orphan drug designation by the FDA and EMA, rare pediatric disease designation by the FDA, and in January 2021, was granted Fast Track designation by the FDA for the treatment of ACHM caused by *CNGA3* mutations.

AAV-AIPL1 for the Treatment of LCA4

LCA4 is an IRD that causes complete blindness before age five. AIPL1 is a central protein for the maintenance of photoreceptor structure and function. Deletion of the *AIPL1* gene causes the most severe form of early retinal dystrophy, LCA4, in which the retinal structure is destroyed with complete vision loss. LCA4 is rare, representing approximately 8% of all LCA cases.

There are currently no approved treatments for LCA4, and we believe an effective intervention will require introducing a normal functional copy of the *AIPL1* gene into rod and cone photoreceptors early in a patient's life while some retinal structure remains in order to activate function and survival of the photoreceptors that are still present. We believe gene therapy has the potential to be the only effective way to address the disease's root cause.

LCA4's extremely rapid progression, rarity and early age of onset make the standard process of seeking regulatory approval through clinical development challenging because adult safety trials would not yield meaningful data given the early onset of the disease.

To address LCA4, we developed a viral vector to replace the *AIPL1* gene in all photoreceptors by using the *AIPL1* cDNA driven by the rhodopsin kinase promoter, which is active in both rods and cones.

We have manufactured and released AAV-AIPL1 for compassionate use under an MHRA specials license in the UK to treat LCA4 patients. A specials license allows physicians to prescribe a treatment of AAV-AIPL1 for LCA4 patients they deem appropriate. We play no role in the physician's treatment decision. We intend to use any data produced by the compassionate use treatment to inform any potential clinical development plan as well as any interactions with the regulatory agencies that would enable us to make this intervention more widely available to the LCA4 patient population.

As the manufacturer of AAV-AIPL1 under a specials license, we have a record retention requirement and a continuing obligation to inform the MHRA of any suspected adverse reaction to our medicinal product which is a serious adverse reaction.

The UK's Human Medicines Regulations 2012 allow for the manufacture and supply of medicinal products not authorized for marketing to patients with special needs at the request of the healthcare professional responsible for the patient's care (these products are referred to as "specials"). A special may only be supplied in: (i) response to an unsolicited order from a healthcare professional responsible for the care of the patient, (ii) if the product is manufactured and assembled in accordance with the specifications of that healthcare professional to fulfil the special needs of the individual patient that cannot be met by products already authorized for marketing and (iii) if the product is manufactured under a specials license granted by the MHRA.

Manufacturing a special also imposes a five year record retention requirement subject to review by the MHRA, including details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or

subsequently becomes aware, as well as a continuing obligation to notify the MHRA of any suspected adverse reaction to the medicinal product which is a serious adverse reaction.

The FDA and European Commission granted orphan designation to AAV-AIPL1 for treatment of inherited retina dystrophy due to defects in *AIPL1* gene.

Ophthalmology Preclinical Development Pipeline

We also have a preclinical IRD development pipeline focused on diseases caused by mutations in additional genes. In order to expand our gene therapy pipeline for retinal diseases, we are also developing treatments for certain multifactorial eye diseases, which are diseases caused by multiple genetic or environmental factors.

AAV-RDH12 for the Treatment of RDH12 Mutation-Associated Retinal Dystrophy

Disease-causing sequence variants in *RDH12* cause severe retinal dystrophy most often resulting in the clinical diagnosis of Leber congenital amaurosis (LCA) and early onset severe retinal dystrophy (EOSRD); although RDH12 variants have also been associated with a clinical diagnosis of RP. Sequence variants in *RDH12* account for 3.4%–10.5% of LCA/EOSRD. Individuals with RDH12 deficiency exhibit widespread retinal degeneration impacting both rods and cones, with early macular involvement. Most people with RDH12–LCA/EOSRD experience marked central visual loss by their late teens to twenties. AAV-RDH12 is an AAV based gene therapy designed to deliver a functional copy of the *RDH12* gene to the retina of patients with genetically defined RDH12 deficiency.

We received orphan drug designation from the FDA as well as orphan medicinal product designation from the European Commission for AAV-RDH12 for the treatment of RDH12-associated retinal dystrophy.

We currently have an ongoing natural history study for patients with RDH12 mutation-associated retinal dystrophy. This will allow us to collect structural and functional data for up to five years on prospectively defined endpoints including functional tests, retinal imaging and electrophysiological assessments. We believe access to these patients and their data will enable us to efficiently enroll the most appropriate patients into a clinical trial for AAV-RDH12.

Wet and Dry Neovascular Age Related Macular Degeneration (AMD)

We are developing pre-clinical programs relating to neovascular age related macular degeneration, or wet AMD. We use a gene therapy product to deliver an antibody targeting the vascular endothelial growth factor receptor 2, or anti-VEGFR2, with the aim of blocking disease related vascular formation in the eye.

Additionally, we are developing a novel approach to treat advanced dry AMD patients who have lost central vision through our innovative “rod-to-cone” technology. By genetically engineering rods with molecules that will improve their speed of response to light, we aim to effectively transform a patch of rod photoreceptors in the outer part of the retina to behave more like cone photoreceptors, thus improving vision. There is no currently approved therapy that impacts disease progression of dry AMD. The best available treatment for patients after they lose central vision and acuity is support and rehabilitation services to help them better utilize the remaining peripheral part of their retina.

Our Salivary Gland Programs

Our second area of clinical focus is xerostomia, a chronic and debilitating disorder of the salivary glands in which saliva production is impaired. Xerostomia may be caused by a number of different insults to the salivary glands, including radiation therapy for head and neck cancer and certain autoimmune diseases.

AAV-hAQP1 for the Treatment of Radiation-Induced Grade 2/3 Xerostomia

Radiation-induced xerostomia, or RIX, is a severe and debilitating long-term side effect of radiation treatment for head and neck cancer. Chronic RIX results in severe side effects, including difficulty swallowing, or dysphagia, oral discomfort, malnutrition, oral mucositis, changes in taste, increased oral infections and dental cavities, resulting in a significant negative impact on patient quality of life. Current treatment options for RIX are few and are of limited benefit. The sialogogues pilocarpine (approved for RIX) and cevimeline (used off-label) are minimally effective in patients with grade 2/3 RIX where the gland structure and function have been significantly impaired. No new medications for RIX have been approved in over 20 years.

Worldwide, there are approximately 650,000 new cases of head and neck cancer diagnosed each year, with approximately 54,000 cases in the U.S. alone, making it the fifth most common malignancy. Approximately 85% of patients who receive radiation treatment for head and neck cancer experience reduced saliva production during treatment, and approximately 50% of those patients who remain cancer free for two or more years after treatment continue to suffer from grade 2 or 3 RIX. There are approximately 170,000 such patients in the U.S., with approximately 5,000 to 10,000 new cases each year in the U.S.

Salivary glands are an attractive target organ for gene therapy treatments because they are self-contained, partially immune protected and easily accessible, allowing for non-invasive delivery of small vector doses.

We are developing AAV-hAQP1 to treat RIX by increasing water conduction in the chronically damaged salivary glands by introducing a water conducting channel into the remaining epithelial cells of these damaged glands. Adequate water secretion by surviving epithelial cells has the potential to deliver the protective exocrine proteins produced by remaining gland cells into the mouth.

The key to our approach is that, unlike the water conducting acinar cells, the water impermeable duct cells of the glands appear to be resilient to infrared radiation exposure. As a consequence of this relative resilience to radiation treatment, salivary glands damaged by radiation treatment tend to contain mostly water impermeable ductal epithelial cells. To make these duct cells permeable to water, AAV-hAQP1 introduces the gene for the human aquaporin water channel, or *hAQP1*. We have demonstrated that this has the potential to convey water permeability and causes ductal cells to generate an osmotic gradient, which causes them to secrete fluid into the lumen of the duct.

The proof of concept for this mechanism and its ability to increase the volume of saliva secreted by damaged salivary glands was observed in a Phase 1 clinical trial conducted by the NIH in patients with chronic grade 2 or 3 RIX. The trial was designed as a short-term dose escalation trial of a gene therapy using adenovirus as the vector to deliver the *hAQP1* to the remaining epithelial cells in the parotid gland of 11 patients suffering from chronic RIX. There were no reported severe adverse events among the patients treated, two out of three patients in each of the first three cohorts in this clinical trial were observed to have objective increases in saliva volume produced by the treated parotid gland, with increases in parotid flow ranging from 60% to 540%, and all but one of these patients showed a decrease in symptoms of dry mouth as measured by subjective visual analog scales, validated in other forms of xerostomia. The results of this study were published in *Proceedings of the National Academy of Sciences* in 2012.

We are currently conducting a Phase 1 dose escalation clinical trial of AAV-hAQP1 at the NIH in patients with grade 2 or 3 RIX who remain cancer free for at least five years after receiving radiation treatment. In this trial we are using AAV2 to deliver the *hAQP1* gene, as we believe AAV2 efficiently transfects the salivary gland cells and does not spread beyond the target cells. The aim of the trial is to determine the safety of inserting *hAQP1* locally into the salivary glands of RIX patients, as well as to measure changes in salivary flow resulting from the introduction of this channel. This clinical trial is being conducted in conjunction with the National Institute of Dental and Craniofacial Research at the United States National Institutes of Health, or the NIH, Dental Clinic.

In the third quarter of 2019, we also initiated an open-label, multi-center Phase 1 dose escalation clinical trial of a single administration of our product candidate AAV-hAQP1 to one or both parotid glands in patients with grade 2 or 3 RIX. In December 2021, we announced preliminary data from this Phase 1 clinical trial. The announcement included data from seven patients treated in cohorts 1, 2 and 3 of the unilateral dose escalation phase of the clinical trial. Six of the seven patients who reached 90 days following treatment reported their symptoms of dry mouth as better following treatment pursuant to a validated patient reported assessment of xerostomia symptoms, constituting clinically meaningful improvement. One patient who reported the maximum response evaluable at 12-months had reached the 24-month time point and reported the same level of response. In March 2022, we completed enrollment of the study. A total of 24 patients received either unilateral (n=12) or bilateral (n=12) treatment in one of eight escalating dose cohorts of three patients each.

In December 2022, we announced additional positive clinical data from the Phase 1 dose escalation clinical trial of AAV-hAQP1. As of the cutoff date of November 30, 2022, all 12 unilaterally treated participants had undergone their 12-month assessment, with three having completed their 24-month assessment and one having completed their 36-month assessment in the long-term follow-up study. All 12 bilaterally treated participants had undergone their 6-month assessment. The investigational gene therapy AAV-hAQP1 has been well tolerated with no dose limiting toxicity or treatment-related serious adverse events, and improvements have been seen in validated patient reported assessments of xerostomia symptoms and in whole salivary flow rate. All subjects are to be followed for one year post-treatment in the present study and for an additional four years in the long-term follow-up study, per FDA guidelines. The study's primary endpoint is safety. Secondary endpoints include change from baseline in patient reported measures of xerostomia symptoms as well as whole salivary flow rates.

Based on the safety and efficacy profile of AAV-hAQP1 in the Phase 1 clinical trial and regulatory precedent, we intend to initiate a randomized, double-blind, placebo-controlled Phase 2 study evaluating two active doses of AAV-hAQP1 for the treatment of grade 2 or 3 RIX in the first half of 2023.

The FDA granted orphan drug designation to AAV-hAQP1 for the treatment of symptoms of grade 2 and grade 3 late xerostomia from parotid gland hypofunction caused by radiotherapy for cancer of the oral cavity.

AAV-hAQP1 for the Treatment of Sjogren's Syndrome

The destruction of salivary tissue resulting in chronic xerostomia may also be caused by chronic autoimmune disease. Sjogren's syndrome is an autoimmune disease in which a patient's immune system may target the salivary glands. Chronic inflammation of the salivary glands results in long term damage and chronic xerostomia in many Sjogren's patients. Data from preclinical studies in animal models of Sjogren's syndrome and data from explants of minor salivary glands of Sjogren's patients suggest that Sjogren's syndrome may also be treatable with our AAV-hAQP1 vector. Supported by data from our preclinical studies and our ongoing RIX clinical trials, we are currently conducting IND-enabling studies of AAV-hAQP1 for xerostomia caused by Sjogren's syndrome.

Our Neurodegenerative Disease Programs

Neurodegenerative diseases are our third area of focus. Relying on our expertise in viral vector design, delivery, production and manufacturing, we are aiming to develop and optimize vectors to effectively treat both genetic and sporadic forms of these diseases.

AAV-GAD for the Treatment of Parkinson's Disease

Our first target indication is Parkinson's disease, where we have Phase 2 clinical data from a successful randomized, double-blind, sham-controlled trial.

Affecting nearly one million Americans and 10 million worldwide, Parkinson's disease is the second-most common neurodegenerative disease after Alzheimer's disease and is the 14th-leading cause of death in the United States. It is associated with a progressive loss of motor control (e.g., shaking or tremor at rest and lack of facial expression), as well as non-motor symptoms (e.g., depression and anxiety). There is no cure for Parkinson's disease and 60,000 new cases are diagnosed each year in the United States alone.

Our product candidate targeting Parkinson's disease, AAV-GAD, is designed to deliver the glutamic acid decarboxylase, or *GAD*, gene to the subthalamic nucleus in order to increase production of GABA, the primary inhibitory neurotransmitter in the human brain. GAD is the rate-limiting enzyme in the synthesis of GABA, therefore we believe that increasing subthalamic nucleus GAD expression through gene therapy has the potential to address the dysregulation of motor circuits and improve symptoms in Parkinson's disease patients without affecting other brain regions, which can be responsible for complications of existing therapies.

Clinical Development of AAV-GAD

In a blinded Phase 2 clinical trial of AAV-GAD in patients with medically refractory Parkinson's disease, 45 patients were randomized 1:1 to receive either AAV-GAD gene therapy delivered by injection into the subthalamic nucleus on both sides of the brain or bilateral sham surgery. Subjects were followed for one year and all results remained blinded until the final treated patient reached the 6-month primary endpoint. The trial met the primary endpoint, of six-month change from baseline in double-blind assessment of off-medication motor scores of the Unified Parkinson's Disease Rating Scale, or UPDRS. At the six-month endpoint, UPDRS score for the AAV-GAD group decreased by 8.1 points (SD 1.7, 23.1%; $p<0.0001$) and by 4.7 points in the sham group (1.5, 12.7%; $p=0.003$). The AAV-GAD group showed a significantly greater improvement from baseline in UPDRS scores compared with the sham group over the six-month course of the study (RMANOVA, $p=0.04$). An improvement in complications of medical therapy as measured by the UPDRS part 4 was observed in the AAV-GAD group at both six and 12 months. A significant decline in duration of disabling dyskinesia was observed only in the AAV-GAD treated patients.

AAV-GAD was reported to be well-tolerated, with no significant adverse events related to the therapy and no speech or cognitive complications observed. The results of the trial were published in the March 2011 issue of *The Lancet Neurology*, the August 2014 issue of the *Journal of Clinical Investigation* and the April 2017 issue of *JCI Insight*, building upon publications of the Phase 1 trial data in *The Lancet* and the *Proceedings of the National Academy of Sciences*. In addition, in research published in the November 28, 2018 issue of *Science Translational Medicine*, fifteen patients treated with AAV-GAD gene therapy were observed to have expressed a treatment-related reorganization of functional brain connectivity that was related to disease symptom improvement. These flurodeoxyglucose positron emission tomography analyses provided objective biological evidence of improvements in abnormal brain networks associated with Parkinson's disease following AAV-GAD gene therapy.

These results were observed in patients treated in both Phase 1 and Phase 2 studies. Blinded analyses showed significant improvements in abnormal thalamic metabolism, a key node in the movement circuitry, in the AAV-GAD treated patients. This pattern of brain network activity was not seen in untreated hemispheres or patients in the sham arm. Furthermore, a specific pattern of brain network activity was identified in those subjects with clinical improvements in the sham arm, which was different from the pattern observed in AAV-GAD responders.

We filed an Investigational New Drug application (IND) for AAV-GAD in May 2022, and we are now dosing patients in an AAV-GAD Phase 1 study with material that has been manufactured with our in-house proprietary manufacturing process at our cGMP manufacturing facility in London. The objective of the AAV-GAD trial is to evaluate the safety and tolerability of delivery of AAV-GAD into the subthalamic nuclei of participants with Parkinson's disease.

Neurodegenerative Disease Preclinical Development Pipeline

In addition to our clinical stage Parkinson's disease program, we continue to conduct research to develop our preclinical pipeline of gene therapy product candidates for the treatment of other serious diseases of the central nervous system, including AAV-UPF1 to address motor neuron death in ALS, and an Alzheimer's disease program focused on endosomal trafficking dysfunction. Each of these programs are directed towards the underlying cell biology that may be driving neurogeneration in these diseases.

ALS

ALS is a devastating, progressive, neurodegenerative disease leading to the loss of motor neurons, which are the neurons that control the ability to move, speak, swallow and ultimately to breathe. The gradual paralysis in ALS invariably leads to death. While 10% of ALS cases are caused by inherited genetic mutations, most ALS occurs sporadically, with no known genetic cause. Mutations in over 20 genes have been identified that cause the inherited ALS cases. Characterization of these disease-causing genes have implicated several cellular pathways in the disease, with a prominent role emerging for genes involved in the cellular control of RNA. Many new regulatory roles are being discovered for RNA, particularly in neurons.

We have designed a viral vector product candidate, AAV-UPF1, with the aim of increasing *UPF1* expression in the motor neurons of ALS patients. In preclinical studies, we observed that administration of AAV-UPF1 reduced motor neuron death thought to be driven by the toxic effects of several different genetic causes of ALS including, TDP-43, FUS and C9*orf*72. Improvements in ALS-like symptoms related to limb strength and mobility in rodent models of ALS have also been observed following administration of AAV-UPF1.

We believe that gene therapy using AAV-UPF1 may increase *UPF1* levels in cells affected by ALS, and we intend to deliver our viral vector product candidate to the central nervous system via intrathecal injection, or injection into the spinal canal.

Alzheimer's Disease

With the world population aging, Alzheimer's disease has emerged as an extremely common and costly disease. While some treatments that have temporary effects on Alzheimer's disease symptoms are available, there is currently no approved treatment that halts the progression of the disease.

Our Alzheimer's disease program focuses on the endosomal trafficking pathway. In preclinical studies, we observed that increasing levels of key retromer proteins may reverse endosomal trafficking defects. We are identifying suitable retromer targets for gene augmentation in pre-symptomatic Alzheimer's patients.

There are several reasons why gene therapy is, in principle, well suited for Alzheimer's disease and other neurodegenerative diseases. The first relates to the pathophysiology, time course, and anatomical spread of these disorders. Neurodegenerative diseases generally begin locally in selectively vulnerable regions with "cell sickness" years before rampant cell death and wide-spread anatomical distribution. To be most effective, we believe interventions should be administrated early and will benefit from local delivery. Even then, however, an intervention must maintain its efficacy for years because, unlike other cells in the body, neurons do not typically divide over the course of their life. We believe AAV-delivered gene therapy products may have a durable effect. In the best case scenario, one delivery successfully taken up by targeted neurons would be sufficient for years of efficacy.

An important component of our approach is the development and validation of surrogate markers of endosomal dysfunction and predictive markers of Alzheimer's disease. In particular, several well studied biomarkers linked to Alzheimer's disease, such as amyloid-beta and tau, have also been shown to be biomarkers of endosomal trafficking dysfunction in neurons. Such biomarkers could potentially be used to identify patients with Alzheimer's disease, as well

as demonstrate potential product efficacy in the absence of Alzheimer's disease symptoms. By targeting endosomal trafficking dysregulation we aim to address the underlying cause of Alzheimer's disease as well as other neurodegenerative diseases, such as certain forms of Parkinson's disease.

Our Strengths

In addition to our three core therapeutic areas of focus, our six ongoing clinical development programs, and our broad pipeline of preclinical programs, we have core capabilities in viral vector design and optimization, gene therapy manufacturing and a potentially transformative gene regulation platform technology that allows precise, dose responsive control of gene expression by oral small molecules with dynamic range that can exceed 5000-fold. Utilizing the following key strengths, we aim to develop, commercialize and expand our portfolio of product candidates.

- **Deep Expertise in Gene Therapy Development:** We believe our expertise in viral vector design, optimization and process development allows us to efficiently advance gene therapy products candidates from preclinical development to cGMP manufacturing and clinical development through commercialization.

- **Potentially Transformative Gene Regulation Platform Technology:** We are developing proprietary technology to enable innovative gene therapy treatments whose expression can be turned on and off with an easily administered small molecule. We believe the capacity for temporal control of gene therapy products has the potential to transform the gene therapy landscape by opening up new treatment possibilities.

- **Manufacturing Capabilities and Capacity:** We have a flexible and scalable cGMP manufacturing facility and production process in London, which we expect can supply our current clinical and preclinical programs through regulatory approval and, should they be approved, provide sufficient capacity for their commercial production. We have also expanded our manufacturing capabilities with our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland. Coming online in 2022 and stretching over 150,000 square feet, it is the first commercial-scale gene therapy manufacturing site in Ireland and is unique in its scale and integrated capabilities. The site contains three facilities, one built to be flexible and scalable for viral vector production for clinical and commercial supply, in addition, a facility to manufacture plasmid DNA – the critical starting material for producing gene therapy products – and thirdly, a QC hub performing advanced biochemical quality control testing for our clinical and commercial programs.

- **Robust and Diverse Clinical and Preclinical Pipeline:** Applying our portfolio approach to gene therapy product development, our initial focus is on treatments for ocular disorders, including IRDs and large degenerative ocular diseases, as well as salivary gland disorders and neurodegenerative diseases. We have six programs in clinical development, one program under a compassionate use specials license and a broad preclinical development pipeline.

- **Relationships with Leading Institutions:** Our longstanding relationships with leading institutions and experts provides us with guidance on development strategy and access to potential patients for our clinical trials.

- **Natural History Study Data:** We sponsor ongoing prospective long-term natural history studies in IRDs that facilitate our ability to efficiently enroll our treatment studies, potentially reducing clinical trial timelines and providing insight into the appropriate endpoints for regulatory approval.

Our Strategy

Our goal is to develop and commercialize innovative gene therapy products to treat serious disorders and broaden the scope of indications that may be treatable by our gene therapies. Our strategy to achieve this goal is to:

- successfully complete clinical development, obtain regulatory approval and commercialize our pipeline of gene therapy product candidates;
- continue to advance the development of our preclinical pipeline product candidates;
- utilize our viral vector design and optimization capabilities to identify and develop new gene therapies for serious diseases;
- advance the development of our potentially transformative proprietary technology for regulating the activity of gene therapy products using small molecules and initiate clinical trials of new regulatable product candidates; and
- continue to pursue and evaluate further strategic collaborations with additional biotechnology and pharmaceutical companies to leverage our capabilities, manufacturing capacity and proprietary gene regulation technology.

Gene Therapy Overview

Gene therapy uses a delivery vehicle, referred to as a vector, to insert a functionally active gene into cells in the body. The gene encodes a therapeutic protein that may block disease pathways or may enhance a deficient pathway. Gene therapy has been studied for over 50 years, with a variety of different viral vectors employed to deliver therapeutic genes. Since the first clinical study of therapeutic gene transfer in humans in 1990, thousands of gene therapy studies covering a broad range of disease targets have been initiated. In recent years, the first gene therapies have received regulatory approval, including approval by the FDA of Luxturna, marketed by Spark Therapeutics, Inc. which was purchased by Roche, for treatment of *RPE65*-associated retinal dystrophy, and Zolgensma, marketed by AveXis, Inc., a Novartis company, for the treatment of spinal muscular atrophy, resulting in a growing acceptance of gene therapy technology as a potentially safe and effective therapeutic approach.

Our current programs use adeno-associated virus, or AAV, as the vector for delivering gene sequences into a patient's cells. The key components of an AAV vector include: (i) the capsid, or the outer viral protein shell that encloses the target DNA, which is responsible for binding to the cell surface and allowing the therapeutic gene that it is carrying to enter the cell; (ii) the therapeutic gene, or transgene, that encodes the therapeutic protein; and (iii) the promoter, or the DNA sequence that drives the expression of the transgene. AAV is a good vector for gene therapy delivery because of its relative safety and broad applicability. AAV is less immunogenic, or less prone to causing an immune reaction, than previous generations of gene therapy vectors, such as adenoviral vectors and AAV does not readily integrate into the genome of the target cell, reducing the potential for oncogenesis, or the induction of cancer. AAV vectors can transfer a therapeutic gene into, or transduce, numerous cell types. Slight differences in capsid proteins can modulate the efficiency with which different capsids deliver genes to different cells, thus allowing different AAV capsids to be selected to most effectively target particular cell types.

The therapeutic gene sequence that enters the targeted cell includes both the protein coding region and an engineered promoter sequence that is used to drive functional gene expression. These engineered promoters may be designed to drive different levels of gene expression or to limit gene expression to specific cell types. Additional aspects of the transgene sequence may be engineered for optimal gene expression, such as codon usage and synthetic introns, which may enhance levels of therapeutic protein expression.

Gene therapy can be used to address monogenic diseases, which result in mutations in a single gene in a patient's genome. In such cases, the viral vector is used to deliver a normal copy of the gene to the cells that are defective due to the lack of the gene function. The normal gene then drives production of the missing protein and offers a therapeutic benefit in patients with the disease. This gene replacement approach underlies all of our IRD programs.

In addition to replacing a gene that is defective or missing in a monogenic disease, gene therapy can also provide a therapeutic impact by adding a particular new gene function to cells and thereby change cell behavior and function in other types of diseases. This is the aim of our salivary gland programs, where our treatment is designed to promote water to flow through otherwise impermeable cells in damaged salivary glands and increase saliva flow into the mouth. Additionally, gene therapy may be used to deliver a therapeutic protein that may block a disease pathway or enhance a deficient cellular pathway in multifactorial diseases such as wet AMD and neurodegenerative diseases, including ALS and Alzheimer's disease.

Importantly, AAV vectors enable targeting of therapeutic genes to non-dividing cells, in which they are thought to remain for the rest of the cell's life. This means that a single treatment may offer patients a durable effect and long-term benefit. The specific cells of the eye, salivary gland and the neurons that we target in our current gene therapy programs are largely non-dividing cells and preclinical evidence has shown that they can be effectively targeted by the specific AAV capsids that we use, enabling us to potentially achieve a durable impact on each of the diseases that we treat.

Our Competitive Advantage in IRDs: Vector Engineering, Natural History Studies and Relationships with Leading Institutions

IRDs as a class are the most common cause of blindness in the working age population worldwide and a leading cause of impaired vision in children in developed countries. There are approximately 200,000 people in each of the U.S., EU and UK affected by IRDs. However, IRDs may be caused by mutations in over 300 identified genes, and in many cases each genetically defined IRD may be a small patient population. Meaningful clinical trials for these sorts of rare indications are especially challenging because they require access to sufficient patients and baseline data on each patient in order to secure clear indicators of efficacy as a result of intervention. We seek to address this problem by sponsoring prospectively designed natural history studies in each of the indications that we are treating in our Phase ½ trials.

For each of the natural history studies, baseline assessments are made upon enrollment, with follow up assessments at later time points. A broad range of assessments are used, including functional tests, retinal imaging and electrophysiological assessments. The same assessments used for each natural history study are used in our corresponding clinical trial targeting the same indication, allowing us to compare the impact of our product candidates on the progression of these diseases on a population, as well as individual patient basis.

We expect the natural history studies will enhance our understanding of disease progression for each indication that we are targeting and allow us to identify optimal windows for intervention, provide specific functional and structural parameters to quantify treatment effects and define clinical endpoints. These studies also provide us with a source of potential patients for our treatment studies and have facilitated efficient enrollment of these studies. These patients are not only genotyped, but also have up to five years of detailed functional and structural assessment data prior to enrollment into an appropriate treatment study.

We also have longstanding active relationships and clinical site agreements with leading institutions in retinal disorder treatments, including, among others, Moorfields Eye Hospital in London, the University of Michigan Kellogg Eye Center, Massachusetts Eye and Ear, the Medical College of Wisconsin & Froedtert Hospital and the Casey Eye Institute at the Oregon Health & Science University. These institutions and others where we have active relationships are among the premier treatment centers for the indications that we are pursuing and provide us with access to potential patients for our clinical trials and experts in IRDs who offer strategic guidance and expertise for our development

strategy. They provide services with respect to our preclinical and clinical studies. Participants enrolled at the University of Michigan Kellogg Eye Center and Massachusetts Eye and Ear Hospital may travel to the Medical College of Wisconsin & Froedtert Hospital for adaptive optic assessments. The Casey Eye Institute at the Oregon Health & Science University provides certain reading center and other clinical services with respect to our clinical trials.

Our Gene Regulation Platform

We are developing a potentially transformative technology designed to precisely and specifically control gene therapy expression levels via dose-response to orally delivered small molecules. The aim of this gene regulation platform is to transform gene therapy into a generalizable mechanism for the delivery of biologic drugs. The idea is that the gene encoding a particular biologic drug or a therapeutic antibody would be delivered to target cells in the body, but these genes would only be activated in the presence of a specific, proprietary small molecule. The therapeutic protein would be manufactured by the body only in the presence of the small molecule so that intermittent production of the therapeutic protein would be achieved by dosing with the small molecule drug.

This temporal regulation of gene therapy products by exogenous small molecules has long been a goal of gene therapy researchers. The ability to regulate transgenes by introducing temporal control has the potential to transform the gene therapy landscape and the biologics industry as a whole. Our approach focuses on riboswitches to regulate gene expression rather than on the modulation of transcription factor activity.

Riboswitches are pieces of RNA that fold into alternative shapes depending on the binding of a specific small molecule to that RNA sequence. One RNA shape allows the gene containing the riboswitch to be active, while the alternative shape inactivates the gene. Riboswitches are used extensively by bacteria, but none have been identified in mammalian cells to date.

We designed *de-novo* mammalian riboswitches that we have observed respond to small molecules to switch genes on and off in mammalian cells and *in vivo* in mice. Our riboswitch contains a stretch of RNA sequence, called an aptamer, that binds to a specific small molecule. The riboswitch is inserted into the therapeutic transgene cDNA. In the absence of the specific small molecule, the unbound riboswitch folds into the shape that drives the destruction of the RNA message and no therapeutic protein is produced in the absence of the small molecule. However, when the small molecule is present and binds to the riboswitch it adopts the alternative RNA shape, causing stable messages to be formed and the therapeutic protein to be produced.

One of the features of our mammalian riboswitch is its unprecedented dynamic range of greater than 5,000-fold. We believe this technology is viable for a therapeutic product and is also the first instance of a proprietary system for screening randomized aptamers and small molecules within mammalian cells for functional interactions.

Using our proprietary technology, we have demonstrated the ability to regulate multiple genes *in vitro* and *in vivo* in multiple tissue types using multiple small molecules.

Our Manufacturing Capabilities

We own and operate a cGMP manufacturing facility situated in London, United Kingdom. Supporting our global approach to clinical development and market supply, we designed the 29,000 square foot facility to meet multiple regulatory standards, including the MHRA, EMA and FDA standards.

We believe our facility can supply our current clinical and preclinical programs through regulatory approval and, should they be approved, provide sufficient capacity, for commercial production. Strategically, we believe our facility will minimize our dependence on third-party CMOs, which we believe provides a significant strategic, clinical and commercial advantage.

Our London facility is flexible and scalable, with eleven independent air handling units, two cell culture suites and three separate viral vector production suites, which allows us to produce multiple product candidates in parallel, as well as sequentially at different scales. This allows us to accommodate up to three independent parallel manufacturing streams of viral vector products that are isolated within dedicated production areas.

Our London manufacturing facility includes an integrated analytical department and in-house analytical tool kit that allows for in-house release of clinical and commercial manufactured products. It is also equipped with dedicated areas for microbiology, molecular biology, and cell-based analytics. Our analytical department can perform product related assays, allowing us to retain and gain expertise that is normally lost to third parties. The close integration allows for rapid turnaround and flexibility in scheduling of key assays, reducing lead times for product candidate releases. Further, our dedicated product fill and finish suite allows us to manufacture a full range of clinical and commercial products under one roof and in our control.

We have more than 205 highly trained multidisciplinary staff on our manufacturing team with backgrounds in a diverse array of manufacturing sciences, technologies, analytics and production working together to expedite delivery of gene therapy products.

We have identified and licensed a proprietary HEK-293 cell line that is well characterized and that we have banked in hundreds of vials. The specific cell line, size of the bank, culture media, and cryopreservation agents have been selected to facilitate bridging between process development platforms and targets. Our HEK-293 cells are suitable for both the adherent culture platform and the bioreactor process. We believe the ability to use the same cell line throughout the product and process development lifecycle will allow us to use a bracketed approach to process validation and comparability, which we believe may reduce the time and costs related to their implementation.

We have expanded our manufacturing capabilities with our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland. We completed the acquisitions of the buildings and long leasehold interest in January 2021. The campus encompasses 150,000 square feet and contains three facilities, one built to be flexible and scalable for viral vector production for clinical and commercial supply, in addition, a facility to manufacture plasmid DNA – the critical starting material for producing gene therapy products – and thirdly, a QC hub performing advanced biochemical quality control testing for MeiraGTx clinical and commercial programs.

We believe that building a second viral vector manufacturing facility and bringing cGMP plasmid and DNA production, as well as QC analytics, in-house provides greater flexibility and efficiency as we advance our product candidates through development, and should they be approved, commercial production.

Our significant investment in the development of our internal manufacturing capacity and expertise to allow for better control over our process development timelines, costs, product quality and intellectual property provides us with a key competitive advantage.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. This is true in the field of gene therapy generally, and in the treatments for our key disease areas. While we believe that the strength of our team, gene therapy expertise, scientific knowledge and intellectual property provide us with competitive advantages, we face competition from several sources, including large and small biopharmaceutical companies, academic research institutions, government agencies and public and private research institutions. Not only must we compete with other companies that are focused on gene therapy, but any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, clinical trials, regulatory approvals and product marketing than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials and acquiring technologies complementary to, or necessary for, clinical programs. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

There are other organizations working to improve existing therapies or to develop new therapies for our initially selected disease indications. Depending on how successful these efforts are, it is possible they may increase the barriers to adoption and success for our product candidates, if approved. These efforts include two product candidates Applied Genetic Technologies Corporation, or AGTC, have in Phase ½ clinical trials to treat ACHM related to *CNGB3* and *CNGA3*, respectively, a product candidate in Phase ½ clinical trials by each of 4D Molecular Therapeutics, Inc. and AGTC to treat XLRP, as well as Luxturna, marketed by Spark Therapeutics, Inc., and has been approved to treat *RPE65*-associated retinal dystrophy. We are not aware of any other gene therapy product candidates in clinical development targeting xerostomia. We are aware of other ALS gene therapies utilizing different treatment mechanisms to treat different genetically defined subsets of ALS patients, as well as gene therapy product candidates being developed for the treatment of Parkinson's disease, including those being developed by Voyager Therapeutics, Inc., Prevail Therapeutics, Inc. and Axovant Sciences Ltd.

We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. We expect any treatments that we develop and commercialize to compete on the basis of, among other things, efficacy, safety, convenience of administration and delivery, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Intellectual Property

Our success depends in large part upon our ability to secure and maintain proprietary protection for our technologies and products and to operate without infringing the proprietary rights of others. Our policy is to protect our proprietary position by, among other methods, filing or collaborating with our licensors to file U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also use other forms of protection, such as confidential information and trademark protection, particularly where we do not believe patent protection is appropriate or obtainable. Our patent portfolio consists of a combination of issued patents and pending patent applications that are owned or licensed from third parties.

As of December 31, 2022, we own, co-own, have an exclusive license, or an exclusive option to license 297 United States and foreign issued or allowed patents and 466 patent applications, pending in the United States and internationally. For any individual patent, the term depends on the applicable law in the country in which the patent is granted. In most countries where we have filed patent applications or in-licensed patents and patent applications, patents have a term of 20 years from the application filing date or earliest claimed non-provisional priority date. In the United States, the patent term is 20 years but may be shortened if a patent is terminally disclaimed over another patent that expires earlier. The term of a U.S. patent may also be lengthened by a patent term adjustment, in order to address administrative delays by the United States Patent and Trademark Office in granting a patent. In the United States, the term of a patent that covers an FDA-approved drug or biologic may be eligible for patent term extension in order to restore the period of a patent term lost during the premarket FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the natural expiration of the patent. The patent term restoration period is generally equal to the regulatory review period for the approved product which period occurs after the date the patent is issued, subject to certain exceptions. Only one patent may be extended for a regulatory review period for any product, and the application

for the extension must be submitted prior to the expiration of the patent. In the future, we may decide to apply for restoration of patent term for one of our currently owned or licensed patents to extend its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant Biologics License Application.

Company-Owned Intellectual Property

We own eight patent families relating to gene regulation platform technologies developed by us. The first patent family includes 49 issued patents in the United States (two patents), African Regional Intellectual Property Organization, Albania, Australia, Austria, Belgium, Bulgaria, China, Croatia, Cyprus, Czech, Denmark, Estonia, Eurasian Patent Organization, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malaysia, Malta, Mexico, Monaco, Netherlands, North Macedonia, Norway, Philippines, Poland, Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland/Liechtenstein, Turkey and the United Kingdom and 22 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Intellectual Property Organization, Australia, Brazil, Canada, China, Egypt, Eurasian Patent Organization, Hong Kong, India, Indonesia, Israel, Japan, Republic of Korea, Malaysia, Mexico, New Zealand (two applications), Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire February 2, 2036, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The second patent family includes two issued patents in the United States and China and 23 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Intellectual Property Organization, Australia, Brazil, Canada, Egypt, Eurasian Patent Organization, Hong Kong, India, Indonesia (two applications), Israel, Japan, Republic of Korea, Malaysia, Mexico, New Zealand, Philippines (two applications), Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire February 2, 2037, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The third patent family includes two issued patents in Indonesia and Japan and 20 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Intellectual Property Organization, Australia, Brazil, Canada, China, Egypt, Eurasian Patent Organization, Hong Kong, India, Israel, Republic of Korea, Malaysia, Mexico, New Zealand, Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire February 2, 2037, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The fourth patent family includes two issued patents in the United States and Japan and 22 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Industrial Property Organization, Australia, Brazil, Canada, China, Egypt, Eurasian Patent Organization, Hong Kong, India, Indonesia, Israel, Republic of Korea, Malaysia, Mexico, New Zealand (two applications), Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire August 3, 2037, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The fifth patent family includes one issued patent in Japan and 21 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Industrial Property Organization, Australia, Brazil, Canada, China, Eurasian Patent Organization, Egypt, Hong Kong, Indonesia, Israel, India, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire on March 2, 2038, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The sixth patent family includes one issued patent in Japan and 21 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Industrial Property

Organization, Australia, Brazil, Canada, China, Eurasian Patent Organization, Egypt, Hong Kong, India, Indonesia, Israel, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire on February 21, 2038, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The seventh patent family includes 21 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, African Regional Industrial Property Organization, Australia, Brazil, Canada, China, Eurasian Patent Organization, Egypt, India, Indonesia, Israel, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire on March 24, 2041, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

The eighth patent family includes one pending Patent Cooperation Treaty patent application with claims directed to compositions of matter and methods of use. Patents issued from this family are expected to expire on December 15, 2042, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

Licensed Intellectual Property

Certain of our issued patents and pending patent applications are exclusively licensed to us from UCL Business, Plc ("UCLB"), Brandeis University ("Brandeis") and the National Institute of Dental and Craniofacial Research ("NIDCR").

UCLB

The UCLB portfolio includes three licensed patent families relating to our *RPE65*, *CNGA3*, and *RPGR* gene therapy programs and one optioned patent family relating to our dry AMD gene therapy program with a combined 100 United States and foreign issued patents and 53 pending patent applications.

The first patent family, with claims directed to compositions of matter and methods of use relating to our *RPE65* program, and the AAV-RPE65 product candidate includes 43 issued patents in the United States, Albania, Australia, Austria, Belgium, Bulgaria, China, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Mexico, Monaco, Netherlands, North Macedonia, Norway, Philippines, Poland, Portugal, Romania, San Moreno, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland/Liechtenstein, Turkey and the United Kingdom and 13 pending patent applications in the United States, Europe, Brazil, Canada, Egypt, Hong Kong, Israel, Malaysia, Mexico, New Zealand (two applications), Nigeria and Thailand. Patents issued from this family are expected to expire February 8, 2036, not including any patent term extensions or adjustments that may extend the patent term in certain jurisdictions.

The second patent family includes 22 pending patent applications with claims directed to compositions of matter and methods of use relating to our achromatopsia program and the AAV-CNGA3 product candidate in the United States, Europe, African Regional Intellectual Property Organization, Australia, Brazil, Canada, China, Egypt, Eurasian Patent Convention, Hong Kong, India, Indonesia, Israel, Japan, Republic of Korea, Malaysia, Mexico, New Zealand, Philippines, Singapore, South Africa and Vietnam. Patents issued from this family are expected to expire January 14, 2039, not including any patent term extensions or adjustments that may extend the patent term in certain jurisdictions.

The third patent family, with claims directed to compositions of matter and methods of use relating to our retinitis pigmentosa program and the botaretigene sparoparvovec product candidate, includes 42 issued patents in the United States (two patents), Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan (three patents), Latvia, Lithuania, Luxembourg, Malta, Monaco, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, San Moreno, Serbia, Slovakia, Slovenia,

Spain, Sweden, Switzerland/Liechtenstein, Turkey and the United Kingdom and four pending applications in Europe, Canada, China and Hong Kong. Patents issued from this family are expected to expire July 17, 2035, not including any patent term extensions or adjustments that may extend the patent term in certain jurisdictions.

The fourth patent family which we have optioned, with claims directed to compositions of matter and methods of use relating to our dry AMD gene therapy program, includes 11 issued patents in Australia, Canada, Indonesia, Israel, Japan, Republic of Korea, Malaysia, New Zealand, Nigeria, Singapore and South Africa and 14 pending applications in the United States, Europe, African Regional Intellectual Property Organization, Australia, Brazil, China, Eurasian Patent Organization, Hong Kong (two applications), Mexico, Philippines, Singapore, Thailand and Vietnam. Patents issued from this family are expected to expire February 19, 2036, not including any patent term extensions or adjustments that may extend the patent term in certain jurisdictions.

Brandeis

The licensed Brandeis portfolio includes one patent family with claims directed to compositions of matter and methods of use relating to our ALS gene therapy program and the AAV-UPF1 product candidate.

This patent family includes 17 issued patents in the United States (two patents), Austria, Australia, Belgium, Denmark, France, Germany, Hong Kong, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland/Liechtenstein and the United Kingdom and four pending patent applications in the United States, Europe, Canada and Hong Kong. Patents issued from this family are expected to expire October 8, 2033, not including any patent term extensions or adjustments that may extend the patent term in certain jurisdictions.

National Institute of Dental and Craniofacial Research

The exclusively licensed NIDCR portfolio includes one patent family with claims directed to compositions of matter and methods of use relating to our Sjogren's Syndrome gene therapy program. This patent family includes 16 issued patents in the United States, Canada, Australia, Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom. Patents issued from this family are expected to expire August 30, 2033, not including any patent term extensions or adjustments that may extend the patent term in certain jurisdictions.

License Agreements

License Agreements with UCLB

We previously entered into several license agreements with UCLB, covering the following inherited retinal disease programs: (a) ACHM caused by mutations in CNGB3; (b) ACHM caused by mutations in CNGA3; (c) XLRP; and (d) RPE65-mediated IRD (together, the "Licensed Gene Therapy Programs"). The terms of these license agreements were set forth in (i) the license agreement, dated February 4, 2015, as amended, between Athena Vision Ltd. and UCLB (the "First UCLB License Agreement"); (ii) the license agreements, dated July 29, 2017, as amended, between MeiraGTx UK II Limited and UCL Business, Plc (the "Second UCLB License Agreement"); and (iii) the license agreement, dated March 15, 2018, among MeiraGTx Limited, MeiraGTx UK II Limited and UCL Business Plc (the "Third UCLB License Agreement" and, collectively, the "prior UCLB license agreements"). In January and February 2019, we amended and restated the prior UCLB license agreements to establish a new standalone license agreement (each, a "Stand-Alone UCLB Agreement") for each of the Licensed Gene Therapy Programs. We have removed from each of the Stand-Alone UCLB Agreements our obligation to pay UCLB a share of certain sublicensing revenues as was provided under the First UCLB License Agreement and have aligned the material terms of the Stand-Alone UCLB Agreements to track those under the Third UCLB License Agreement as previously disclosed and a summary of which is set forth below as is now reflected in each of the Stand-Alone UCLB Agreements.

Under the terms of the Third UCLB License Agreement, we paid an initial upfront payment of £6,994, and issued to UCLB £100,000 of our ordinary shares.

Under each of the Stand-Alone UCLB Agreements, UCLB granted us an exclusive, worldwide, and sublicensable license under certain intellectual property rights controlled by UCLB relating to one of the Licensed Gene Therapy Programs to develop and commercialize licensed products in a relevant field of gene therapy. We must use diligent efforts to develop and commercialize the licensed products.

Under the terms of each Stand-Alone UCLB Agreement, we are required to pay UCLB sales milestone payments of up to a total of £39.8 million in the aggregate and an annual management fee of £50 thousand until certain royalty payments have been paid. Additionally, pursuant to the Stand-Alone UCLB Agreement related to CNGB3, we paid UCLB an upfront payment of £1.5 million and issued £1.5 million of the Company's ordinary shares.

Commencing on the first commercial sale of licensed products under each Stand-Alone UCLB Agreement, we must make low single-digit percentage royalty payments to UCLB on net sales of such products. Our royalty obligations under each agreement continue on a licensed product-by-licensed product and country-by-country basis until the latest to occur of the expiration of the last valid claim of a patent claiming such licensed product in such country, the expiration of any regulatory exclusivity for all licensed products in such country, or the tenth anniversary of first commercial sale of such licensed product in such country.

Each Stand-Alone UCLB Agreement will remain in effect on a country-by-country basis until the expiration of the last payment obligation in such country. Each Stand-Alone UCLB Agreement may be terminated: (a) by either party in the event of the other party's material breach that remains uncured for 30 days (or for 14 days in the case of breaches related to payment obligations), (b) by either party for the other party's insolvency, (c) immediately by UCLB if we are in persistent breach of the agreement and the parties fail to agree upon a mechanism to remedy such persistent breach (or we do not comply with such agreed upon mechanism), or (d) immediately by UCLB if we undergo certain change of control events or if we enter into a sublicense with certain prohibited persons, which may adversely affect UCL's and/or UCLB's reputation. Each Stand-Alone UCLB Agreement may also be terminated or converted to a non-exclusive license by UCLB upon three months' notice if we, based on an independent expert determination, fail to use diligent efforts to develop and commercially exploit licensed products and do not cure such failure within a certain cure period.

License Agreement between BRI-Alzan Inc. and Brandeis

In May 2013, BRI-Alzan Inc., or BRI-Alzan, entered into a license agreement with Brandeis, or the Brandeis Agreement. On December 31, 2015, we entered into an Agreement and Plan of Merger, or the BRI-Alzan Merger Agreement, with BRI-Alzan, and the Brandeis Agreement was assigned to us as a result of such merger. Pursuant to the terms of the BRI-Alzan Merger Agreement, we agreed to make cash payments to the sellers of BRI-Alzan upon the achievement of certain milestones, subject to an aggregate cap of $4,500,000. In addition, we agreed to make low single-digit percentage royalty payments to the sellers of BRI-Alzan on net sales of any product for the therapeutic or prophylactic treatment of ALS that is covered by a valid claim of the patent rights licensed under the Brandeis Agreement. The BRI-Alzan Merger Agreement includes customary confidentiality, indemnification, non-competition and non-solicitation provisions.

Pursuant to the Brandeis Agreement, Brandeis granted us an exclusive, worldwide license under certain patent rights with claims directed to compositions of matter and methods of use relating to our ALS gene therapy program and the AAV-UPF1 product candidate to develop and commercialize licensed products.

We must use commercially reasonable efforts to develop and commercialize licensed products. We also acquired non-exclusive, worldwide licenses to certain know-how controlled by Brandeis to exploit licensed products. We are required to pay Brandeis developmental and regulatory milestone payments of up to a total of $1.0 million in the aggregate. We are also required to pay Brandeis annual license maintenance fees ranging from $15,000 to $100,000

depending on the development stage of the licensed product. Commencing on the first commercial sale of licensed products, we must make low single-digit percentage royalty payments to Brandeis on net sales of such products. In addition, we must pay Brandeis mid-teen percentages of sublicensing revenues.

The Brandeis Agreement will remain in effect on a country-by-country basis until the earlier of: (a) 1 year after the date that we, our affiliates or sublicensees last sell any licensed product in such country or (b) until the expiration of the last–to-expire of the licensed patent rights in such country. The Brandeis Agreement may be terminated by Brandeis for our insolvency or for our material breach that remains uncured for 60 days (or for 30 days in the case of breaches related to payment obligations). Such material breach may be cured only once in any 12-month period. Brandeis may also terminate any license granted under the Brandeis Agreement if we fail to timely achieve certain regulatory milestone events.

Trade Secrets

We also rely on trade secrets, technical know-how and continuing innovation to develop and maintain our competitive advantage. We require inventors who are identified on any company-owned patent applications to assign rights to us. We also rely on confidentiality agreements with our employees, consultants and other advisors to protect our proprietary information. Our policy is to require third parties that receive material confidential information to enter into confidentiality agreements with us.

Trademarks

Our trademark MeiraGTx has been registered in the U.S., UK and EU.

Government Regulation and Product Approval

Governmental authorities in the U.S., at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, packaging, promotion, storage, advertising, distribution, marketing, post-approval monitoring and reporting and export and import of products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, are extensive and require the expenditure of substantial time and financial resources.

FDA Approval Process

We expect our product candidates to be regulated as biologics. Biological products, including gene therapy products, are subject to extensive regulation by the FDA under the Federal Food, Drug, and Cosmetic Act, or FDCA, and the Public Health Service Act, or PHSA, and other federal, state, local and foreign statutes and regulations. Both the FDCA and the PHSA and their corresponding regulations govern, among other things, the research, development, safety, testing, packaging, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of biological products.

U.S. Biological Products Development Process

Our products must be approved by the FDA through the Biologics License Application, or BLA, process before they may be legally marketed in the United States. The process required by the FDA before a biologic may be marketed in the United States generally involves the following:

- completion of extensive nonclinical studies, sometimes referred to as preclinical laboratory tests, and preclinical studies and applicable requirements for the humane use of laboratory animals and formulation studies in accordance with applicable regulations, including good laboratory practices, or GLPs;

- submission to the FDA of an IND which must become effective before clinical trials may begin;

- approval by an independent Institutional Review Board, or IRB, or ethics committee at each clinical site before the trial is commenced;

- performance of adequate and well controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;

- submission to the FDA of a BLA for marketing approval that includes substantive evidence of safety, purity, potency and efficacy from results of nonclinical testing and clinical trials;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with cGMP to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity;

- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and

- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLPs. The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing and controls, information about product chemistry, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing, such as reproductive toxicity tests and carcinogenicity in animals, may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, after which human clinical trials may begin unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a biological product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA.

In addition to the IND submission process, sponsors of certain human clinical trials of cells containing recombinant or synthetic nucleic acid molecules, including human gene transfer studies, are subject to evaluation and assessment by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution, pursuant to the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. The IBC assesses the safety of the research and identifies any potential risk to the public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's

control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, the efficacy measurements to be evaluated and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed.

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

- Phase 1. The biological product candidate is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

- Phase 2. The biological product candidate is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.

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

In most cases, the FDA requires two adequate and well controlled Phase 3 clinical trials to demonstrate the safety and efficacy of a biological product. In some instances, a single Phase 3 trial, together with other confirmatory evidence may be sufficient to support a BLA submission. Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire.

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

study at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product candidate has been associated with unexpected serious harm to patients. The FDA and the IRB may also halt, terminate or impose other conditions if either believes the patients are subject to unacceptable risk.

There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Sponsors of clinical trials of FDA-regulated products, including biologics, are required to register and disclose certain clinical trial information, which is publicly available at www.clinicaltrials.gov. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved.

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

U.S. Review and Approval Processes

After the completion of clinical trials of a biological product candidate, FDA approval of a BLA must be obtained before commercial marketing and distribution of the biological product. The BLA must include results of product development, laboratory and animal trials, human trials, information on the manufacture, pharmacology, chemistry and controls of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA must contain data to assess the safety and effectiveness of the biological product candidate for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective.

A sponsor who is planning to submit a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan, or PSP, within sixty days after an end-of-Phase 2 meeting or as may be agreed between the sponsor and FDA. The initial PSP must include, among other things, an outline of the pediatric study or studies that the sponsor plans to conduct, including to the extent practicable study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information, along with any other information specified in FDA regulations. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. PDUFA also imposes an annual program fee for products. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first human drug application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application is also subject to an initial review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA's goal is to complete the review of standard BLAs within ten months after it accepts an application for filing, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process is often significantly extended by FDA requests for additional information or clarification.

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

Before approving a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. To assure cGMP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the BLA, the FDA will issue an approval letter. Under the current PDUFA guidelines, the FDA has committed to reviewing such resubmissions in two or six months of receipt depending on the type of information included.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a REMS, to ensure the benefits of the product outweigh its potential risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. The requirement for a REMS can materially affect the potential market and profitability of the product.

Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. Changes to some of the conditions established in an approved BLA, including changes in indications, product labeling, manufacturing processes or facilities, require submission and FDA approval of a new BLA or BLA supplement before the change can be implemented. A BLA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing BLA supplements as it does in reviewing BLAs. The FDA may require one or more Phase 4 post-market studies or surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs or biologics intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and marketing the drug or biologic for this type of disease or condition will be recovered from its sales in the United States. Orphan drug designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and BLA user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application, including a full BLA, to market the same drug or biologic for the same disease or condition for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer with orphan exclusivity is unable to assure sufficient quantities of the approved orphan-designated product. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. In addition, exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new biological products that meet certain criteria. Specifically, new biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new biologic may request that the FDA designate the biologic as a Fast Track product at any time during clinical development of the product. The FDA must determine if the biologic product candidate qualifies for Fast Track designation within 60 days of receipt of the sponsor's request. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application. In addition, a Fast Track designated product is eligible for more frequent meetings with the FDA to discuss

the biologic product's development plan and ensure collection of appropriate data needed to support approval, and may result in more frequent written communication from the FDA about such things as the design of the proposed clinical trials and use of biomarkers.

In addition, the FDA established a Breakthrough Therapy designation which is intended to expedite the development and review of products that are intended to treat serious or life-threatening diseases or conditions. A Breakthrough Therapy-designated product candidate is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the features of Fast Track designation, as well as more intensive FDA interaction and guidance.

Any product submitted to the FDA for marketing, including a product that has received a Fast Track or Breakthrough Therapy designation, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. An application seeking marketing approval for a biologic product is eligible for priority review if the biologic has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or there is potential for a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new biological product designated for priority review in an effort to facilitate the review. Priority review means the FDA's goal is to take action on an application within six months (compared to 10 months under standard review).

Additionally, a product may be eligible for accelerated approval. Biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval, which means that they may be approved on the basis of adequate and well controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a biological product subject to accelerated approval perform adequate and well-controlled post-marketing Phase 4 clinical trials. Failure to conduct required post-approval trials, or to confirm a clinical benefit during post-marketing trials, will allow the FDA to withdraw the approved biologic product from the market on an expedited basis. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Furthermore, as part of its implementation of the 21st Century Cures Act, the FDA established the Regenerative Medicine Advanced Therapy, or RMAT, designation, to facilitate an efficient development program for, and expedite review of, certain drugs and biological products. A biological product is eligible for RMAT designation if it qualifies as a RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions, and is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the biological product has the potential to address unmet medical needs for such a disease or condition. Like Breakthrough Therapy designation, RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review and priority review. Products granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites. RMAT-designated products that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through the submission of clinical

evidence, clinical trials, patient registries, or other sources of real world evidence (such as electronic health records); through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.

Fast Track designation, priority review, accelerated approval, Breakthrough Therapy designation and RMAT designation do not change the standards for approval but may expedite the development or approval process. Even if these designations are received, the FDA may later decide that a product candidate no longer meets the conditions for qualification.

Post-Approval Requirements

Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to cGMP requirements. Manufacturers are required to comply with applicable requirements in the cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements.

After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

The FDA may require one or more Phase 4 post-market trials or surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies. We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the Internet. Biologics may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP requirements and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in

restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Biosimilars and Exclusivity

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered multiple times to an individual, the biologic and the reference biologic may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation of the abbreviated approval pathway that are still being worked out by the FDA.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products.

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

Other Healthcare Laws and Compliance Requirements

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business, which may constrain the financial arrangements and relationships through which we conduct our research, as well as, sell, market and distribute any products for which we obtain marketing approval. Such laws include, without limitation, federal and state anti-kickback, fraud and abuse, false claims and transparency laws and regulations regarding drug pricing and payments or other transfers of value made to physicians and other licensed healthcare professionals. If their operations are found to be in violation of any of such laws or any other governmental regulations that apply, they may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of operations, exclusion from participation in federal and state healthcare programs, integrity oversight and reporting obligations to resolve allegations of non-compliance and imprisonment.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical or biological product for which we obtain regulatory approval. Sales of any product depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state, and foreign government healthcare programs,

commercial insurance and managed healthcare organizations, and the level of reimbursement for such product by third-party payors. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization.

In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Third party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product. Decreases in third-party reimbursement for any product or a decision by a third-party payor not to cover a product could reduce physician usage and patient demand for the product.

Healthcare Reform

The United States and some foreign jurisdictions are considering or have enacted a number of reform proposals to change the healthcare system. There is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by federal and state legislative initiatives, including those designed to limit the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded health care programs, and increased governmental control of drug pricing.

In March 2010, the Patient Protection and Affordable Care Act, or the ACA, was signed into law, which substantially changed the way healthcare is financed by both governmental and private insurers in the United States, and significantly affected the pharmaceutical industry. The ACA contained a number of provisions of particular import to the pharmaceutical and biotechnology industries, including, but not limited to, those governing enrollment in federal healthcare programs, 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, and annual fees based on pharmaceutical companies' share of sales to federal health care programs.

Since its enactment, there have been judicial, Congressional and executive branch challenges to certain aspects of the ACA. On June 17, 2021, the U.S. 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 for purposes of obtaining health insurance coverage through the ACA marketplace from February 15, 2021 through August 15, 2021. 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.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year, which was temporarily suspended from May 1, 2020 through March 31, 2022, and reduced payments to several types of Medicare providers. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At

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

Additionally, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

U.S. Data Privacy and Security Laws

In the United States, numerous federal and state laws and regulations, including data breach notification laws, health information privacy and security laws, including the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and regulations promulgated thereunder, or collectively, HIPAA, and federal and state consumer protection laws and regulations (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure, and protection of health-related and other personal information could apply to our operations or the operations of our partners. In addition, certain state laws, such as the California Consumer Privacy Act, or CCPA, and the California Privacy Rights Act, or CPRA, govern the privacy and security of personal information, including health-related information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to make compliance efforts more challenging, and can result in investigations, proceedings, or actions that lead to significant penalties and restrictions on data processing.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act of 1977, or FCPA, prohibits U.S. corporations and individuals from engaging in certain activities to obtain or retain business or secure any improper advantage, or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any employee or official of a foreign government or public international organization, or political party, political party official, or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The scope of the FCPA also includes employees and officials of state-owned or controlled enterprises, which may include healthcare professionals in many countries. Equivalent laws have been adopted in other foreign countries that impose similar obligations.

Government Regulation Outside of the United States

In addition to regulations in the United States, we may be subject to a variety of regulations in other jurisdictions, for instance in the UK or EU, governing, among other things, clinical trials, marketing authorizations, post-marketing authorization requirements and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries. In addition, ethical, social and legal concerns about gene therapy, genetic testing, genetic research and gene-editing technology, could result in additional regulations restricting or prohibiting the processes we may use.

Whether or not we obtain FDA approval of a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Non-Clinical Studies and Clinical Trials

Similar to the United States, the various phases of non-clinical and clinical research abroad are subject to significant regulatory controls.

Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical or biological substances. Non-clinical studies must be conducted in compliance with the principles of GLP, as set forth in EU Directive 2004/10/EC. In particular, non-clinical studies, both *in vitro* and *in vivo*, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization, or ICH, guidelines on GCPs, as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. Additional GCP guidelines from the European Commission, focusing in particular on traceability, apply to clinical trials of ATMPs. If the sponsor of the clinical trial is not established within the EU, it must appoint an entity within the EU to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU member states, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

The regulatory landscape related to clinical trials in the EU has been subject to recent changes. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. Unlike directives, the CTR is directly applicable in all EU member states without the need for member states to further implement it into national law. The CTR notably harmonizes the assessment and supervision processes for clinical trials throughout the EU via a Clinical Trials Information System, which contains a centralized EU portal and database.

While the EU Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state in which the clinical trial takes place, to both the competent national health authority and an independent ethics committee, much like the FDA and IRB respectively, the CTR introduces a centralized process and only requires the submission of a single application for multi-center trials. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The CTA must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed.

The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the EU Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by the EU Clinical Trials Directive until

January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR.

Medicines used in clinical trials must be manufactured in accordance with good manufacturing practices, or GMP. Other national and EU-wide regulatory requirements may also apply.

During the development of a medicinal product, the EMA and national regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use, or CHMP. A fee is incurred with each scientific advice procedure. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical trials, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future marketing authorization application of the product concerned.

Marketing Authorizations

In the EU, medicinal products can only be placed on the market after obtaining a marketing authorization, or MA. To obtain regulatory approval of an investigational chemical or biological product in the EU, we must submit a marketing authorization application, or MAA. The process for doing this depends, among other things, on the nature of the medicinal product.

"Centralized MAs" issued by the European Commission, based on the opinion of the EMA, are valid across the entire territory of the EU. The centralized procedure is compulsory for certain types of product candidates, such as: (i) medicinal products derived from biotechnology processes, such as genetic engineering, (ii) medicinal products containing a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions and viral diseases, (iii) designated orphan medicines and (iv) ATMPs, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The centralized procedure is optional for product candidates containing a new active substance not yet authorized in the EU, or for product candidates that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

The Committee for Advanced Therapies, or CAT, is responsible in conjunction with the CHMP for the evaluation of advanced therapy medicinal products, or ATMPs. The CAT is primarily responsible for the scientific evaluation of ATMPs and prepares a draft opinion on the quality, safety and efficacy of each ATMP for which an MAA is submitted. The CAT's opinion is then taken into account by the CHMP when giving its final recommendation regarding the authorization of a product in view of the balance of benefits and risks identified. Although the CAT's draft opinion is submitted to the CHMP for final approval, the CHMP may depart from the draft opinion, if it provides detailed scientific justification. The CHMP and CAT are also responsible for providing guidelines on ATMPs and have published numerous guidelines, including specific guidelines on gene therapies and cell therapies. These guidelines provide additional guidance on the factors that the EMA will consider in relation to the development and evaluation of ATMPs and include, among other things, the preclinical studies required to characterize ATMPs; the manufacturing and control information that should be submitted in an MAA; and post-approval measures required to monitor patients and evaluate the long term efficacy and potential adverse reactions of ATMPs. Although these guidelines are not legally binding, we believe that our compliance with them is likely necessary to gain and maintain approval for any of our product candidates.

Under the centralized procedure, the maximum timeframe for the evaluation of an MAA by the EMA is 210 days. This excludes so-called clock stops, during which additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. At the end of the review period, the CHMP provides an opinion to the European Commission. If this opinion is favorable, the Commission may then adopt a decision to grant an MA.

"National MAs" are issued by the competent authorities of the EU member states, only cover their respective territory, and are available for product candidates not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in an EU member state, this national MA can be recognized in another member state through the mutual recognition procedure. If the product has not received a national MA in any member state at the time of application, it can be approved simultaneously in various member states through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the competent authorities of each of the member states in which the MA is sought, one of which is selected by the applicant as the reference member state.

MAs have an initial duration of five years. After these five years, the authorization may be renewed on the basis of a reevaluation of the risk-benefit balance. Once renewed, the MA is valid for an unlimited period unless the European Commission or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal

In exceptional cases, the CHMP might perform an accelerated review of an MAA in no more than 150 days (not including clock stops). Innovative products that target an unmet medical need and are expected to be of major public health interest may be eligible for a number of expedited development and review programs, such as the PRIME scheme, which provides incentives similar to the Breakthrough Therapy designation in the U.S. PRIME is a voluntary scheme aimed at enhancing the EMA's support for the development of medicines that target unmet medical needs. It is based on increased interaction and early dialogue with companies developing promising medicines, to optimize their product development plans and speed up their evaluation to help them reach patients earlier. Product developers that benefit from PRIME designation can expect to be eligible for accelerated assessment but this is not guaranteed. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated contact and rapporteur from the CHMP is appointed early in the PRIME scheme facilitating increased understanding of the product at EMA's committee level. An initial meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Moreover, in the EU, the European Commission may grant a so-called "conditional MA" prior to obtaining the comprehensive clinical data required for an application for a full MA. Such conditional MAs may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive, (ii) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (iii) the product fulfills an unmet medical need and (iv) 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 are still required. A conditional MA may contain specific obligations to be fulfilled by the MA holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional MAs are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The MA can be converted into a standard MA once the MA holder fulfils the obligations that were imposed and the complete data confirm that the medicine's benefits continue to outweigh its risks. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional MA.

The European Commission may also grant a so-called "marketing authorization under exceptional circumstances". Such MA is intended for products for which the applicant can demonstrate that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use even after the product has been authorized, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of

medical ethics to collect such information. Consequently, MAs under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the applicant must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;

- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorized person; and

- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

An MA under exceptional circumstances is subject to annual review to reassess the risk-benefit balance in an annual reassessment procedure. Continuation of the authorization is linked to the annual reassessment and a negative assessment could potentially result in the MA being suspended or revoked. The renewal of an MA of a medicinal product under exceptional circumstances, however, follows the same rules as a "normal" MA. Thus, an MA under exceptional circumstances is granted for an initial five years, after which the authorization will become valid indefinitely, unless the EMA decides that safety grounds merit one additional five-year renewal. An MA under exceptional circumstances should not be granted when a conditional MA is more appropriate.

The EU medicines rules expressly permit the EU member states to adopt national legislation prohibiting or restricting the sale, supply or use of any medicinal product containing, consisting of or derived from a specific type of human or animal cell, such as embryonic stem cells. While the products we have in development do not make use of embryonic stem cells, it is possible that the national laws in certain EU member states may prohibit or restrict us from commercializing our products, even if they have been granted an MA.

Data and Marketing Exclusivity

The EU also provides opportunities for market exclusivity. Upon receiving MA, reference products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from relying on the preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until ten years have elapsed from the initial MA of the reference product in the EU. The overall ten-year market exclusivity period may be extended to a maximum of eleven years if during the first eight years of those ten years, the MA holder obtains an authorization for one or more new therapeutic indications with significant clinical benefit over existing therapies. However, there is no guarantee that a product will be considered by the EU regulatory authorities to be a new chemical or biological entity, and products may not qualify for data exclusivity.

There is a special regime for biosimilars, or biological medicinal products that are similar to a reference medicinal product but that do not meet the definition of a generic medicinal product, for example, because of differences in raw materials or manufacturing processes. For such products, the results of appropriate preclinical or clinical trials must be provided, and guidelines from the EMA detail the type of quantity of supplementary data to be provided for different types of biological product. There are no such guidelines for complex biological products, such as gene or cell therapy medicinal products, and so it is unlikely that biosimilars of those products will currently be approved in the EU. However, guidance from the EMA states that they will be considered in the future in light of the scientific knowledge and regulatory experience gained at the time.

Orphan Medicinal Products

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the United States. A medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition.

Orphan drug designation entitles a party to incentives such as reduction of fees or fee waivers, protocol assistance, and access to the centralized MA procedure. The application for orphan drug designation must be submitted before the MAA. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the MA is submitted. Upon grant of an MA and assuming the requirement for orphan designation are also met at the time the MA is granted, orphan medicinal products are entitled to a ten-year period of market exclusivity for the approved therapeutic indication, which means that regulatory authorities cannot accept another MA or grant an MA or accept an application to extend an existing MA in respect of a similar medicinal product for the same indication for a period of ten years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed pediatric investigation plan, or PIP. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The ten-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity or where the prevalence of the condition has increased above the orphan designation threshold. Additionally, an MA may be granted to a similar product for the same indication at any time if (1) the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior, (2) the applicant consents to a second orphan medicinal product application; or (3) the applicant cannot supply enough orphan medicinal product.

Pediatric Development

In the EU, MAAs for new medicinal products have to include the results of trials conducted in the pediatric population, in compliance with a PIP agreed with the EMA's Pediatric Committee, or PDCO. The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which an MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data are not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the MA is obtained in all EU member states and study results are included in the product information, even when negative, the product is eligible for a six-months supplementary protection certificate extension (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity is granted.

Post-Approval Requirements

Similar to the United States, both MA holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA, the European Commission and/or the competent regulatory authorities of the member states. The holder of an MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance who is responsible for oversight of that system. Key obligations

include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

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

The advertising and promotion of medicinal products is also subject to laws concerning promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each member state and can differ from one country to another.

Failure to comply with EU and member state laws that apply to the conduct of clinical trials, manufacturing approval, MA of medicinal products and marketing of such products, both before and after grant of the MA, manufacturing of pharmaceutical products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials or to grant MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

The aforementioned EU rules are generally applicable in the European Economic Area, or EEA, which consists of the 27 EU member states plus Iceland, Liechtenstein and Norway.

Pricing and Reimbursement

Even if a medicinal product obtains an MA in the EU, there can be no assurance that reimbursement for such product will be secured on a timely basis or at all. Governments influence the price of medicinal products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Member states are free to restrict the range of pharmaceutical products for which their national health insurance systems provide reimbursement, and to control the prices and reimbursement levels of pharmaceutical products for human use. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. Member states may approve a specific price or level of reimbursement for the pharmaceutical product, or alternatively adopt a system of direct or indirect controls on the profitability of the company responsible for placing the pharmaceutical product on the market, including volume-based arrangements, caps and reference pricing mechanisms. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other EU member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low-priced markets exert a commercial pressure on pricing within a country.

Brexit and the Regulatory Framework in the United Kingdom

The UK formally left the EU on January 31, 2020, commonly referred to as “Brexit”. Since the end of the Brexit transition period on January 1, 2021, Great Britain (England, Scotland and Wales) has not been directly subject to

EU laws, however under the terms of the Protocol on Ireland and Northern Ireland, EU laws have generally applied to Northern Ireland. On February 27, 2023, the UK Government and the European Commission reached a political agreement on the "Windsor Agreement" which may revise the Protocol on Ireland and Northern Ireland in order to address some of the perceived shortcomings in its operation. Under the proposed changes, Northern Ireland would be reintegrated under the regulatory authority of the MHRA with respect to medicinal products. These proposed changes need to be codified and agreed by the respective parliaments of the UK and EU before taking effect.

UK Clinical Trials

It is currently unclear to what extent the UK will seek to align its regulations with the EU. The UK regulatory framework in relation to clinical trials is derived from existing EU legislation (as implemented into UK law, through secondary legislation), and after Brexit, EU laws on clinical trials (including the CTR) are no longer directly applicable in Great Britain (i.e., the UK excluding Northern Ireland). On January 17, 2022, the MHRA launched an eight-week consultation on reframing the UK legislation for clinical trials. The consultation closed on March 14, 2022 and aims to streamline clinical trials approvals, enable innovation, enhance clinical trials transparency, enable greater risk proportionality, and promote patient and public involvement in clinical trials. The outcome of the consultation is being closely watched and will determine whether the UK chooses to align with the CTR or diverge from it to maintain regulatory flexibility. Under the terms of the Protocol on Ireland and Northern Ireland, provisions of the CTR which relate to the manufacture and import of investigational medicinal products and auxiliary medicinal products currently apply in Northern Ireland. On February 27, 2023, the UK Government and the European Commission reached a political agreement on the "Windsor Agreement" which may revise the Protocol on Ireland and Northern Ireland in order to address some of the perceived shortcomings in its operation. If implemented, this may have further impact on the application of the CTR in Northern Ireland.

UK Marketing Authorizations

The MHRA is now the UK's standalone regulator for MAAs. All existing centralized procedure MAs were automatically converted into UK MAs effective in Great Britain and issued with a UK MA number on January 1, 2021 (unless MA holders opted out of this scheme by January 21, 2021). As a result of the implementation of the Protocol on Ireland and Northern Ireland, centralized procedure MAs remain valid for marketing products in Northern Ireland. Pending applications which were submitted to EMA prior to the end of the transition period will either be determined in parallel by the MHRA, or will be put "on hold" until the CHMP issues a positive decision which can be relied upon by the MHRA. Converted EU MAs will be treated as if they were granted on the date the corresponding centralized procedure MA was granted and the renewal date will stay the same. If renewals were submitted and no decision was rendered before January 1, 2021, the MHRA will ensure the renewal process is concluded and processed appropriately, and there will be no need to resubmit the application. From January 1, 2021 the requirements for renewal submissions remain the same as required by the EMA and the MA holders should continue to submit renewal applications to the MHRA nine months before they expire (or six months in relation to conditional MAs).

Following January 1, 2021, an applicant for a centralized procedure MA must be established in the EU. After this date, companies established in the UK can no longer use the centralized procedure and instead must follow one of the UK national authorization procedures or one of the remaining post-Brexit international cooperation procedures (such as the Access Consortium) to obtain an MA to market products in the UK. In addition, for a two-year period from January 1, 2021, MHRA may rely on a decision taken by the European Commission on the approval of a new centralized procedure MA when determining an application for a Great Britain MA; or use the MHRA's decentralized or mutual recognition procedures which enable MAs approved in EU member states (or Iceland, Liechtenstein, Norway) to be granted in Great Britain. Additionally, the 'Unfettered Access Procedure' enables MA holders in Northern Ireland to seek recognition in Great Britain. Post Brexit, the MHRA has updated various aspects of the regulatory regime for medicines in the UK, including: introducing the Innovative Licensing and Access Procedure to accelerate the time to market and facilitate patient access for innovative medicines; updates to the UK national approval procedure,

introducing a 150-day objective for assessing applications for MAs in the UK, Great Britain and Northern Ireland and a rolling review process for MA applications (rather than a consolidated full dossier submission).

UK Orphan Designation

Post-Brexit, the UK has retained the EU Regulation which governs the designation of medicinal products as orphan medicinal products and which establishes incentives thereto (Regulation (EC) No. 141/2000) as part of UK law by virtue of the EU (Withdrawal) Act 2018. However under the Retained EU Law (Revocation and Reform) Bill, which is currently before the UK Parliament, unless this legislation is expressly preserved and "assimilated" into domestic law or extended by ministerial regulations (to no later than June 23, 2026) it will automatically expire and be revoked by December 31, 2023. There is therefore uncertainty about the future regulations relating to orphan designation in Great Britain, and any future changes to the legal requirements could lead to greater regulatory complexity and increased costs to our business.

The MHRA is responsible for reviewing applications from companies for orphan designation at the time of a MAA. If a medicinal product has been designated orphan in the EU under Regulation (EC) 141/2000, a Great Britain orphan MAA can be made under regulation 50G of the Human Medicines Regulation 2012 (as amended). A UK-wide orphan MAA can only be considered in the absence of an active EU orphan designation.

If a UK-wide orphan MA is granted and the medicinal product subsequently receives EU orphan designation, the MA holder would need to submit a variation to change this to a Great Britain orphan MA.

UK Specials Regulation

The UK's Human Medicines Regulations 2012 allow for the manufacture and supply of medicinal products not authorized for marketing to patients with special needs at the request of the healthcare professional responsible for the patient's care (these products are referred to as "specials"). A special may only be supplied: (i) in response to an unsolicited order from a healthcare professional responsible for the care of the patient, (ii) if the product is manufactured and assembled in accordance with the specifications of that healthcare professional to fulfil the special needs of the individual patient which cannot be met by products already authorized for marketing, and (iii) if the product is manufactured under a specials license granted by the UK's MHRA.

Manufacturing a special also imposes a five year record retention requirement subject to review by the MHRA, including details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware, as well as a continuing obligation to notify the MHRA of any suspected adverse reaction to the medicinal product which is a serious adverse reaction.

Privacy and Data Protection Laws

We are also subject to laws and regulations in non-U.S. countries in which we are established or in which we run clinical trials, as well as countries in which we may sell, market and distribute products for which we obtain marketing approval. These laws and regulations cover data privacy and the protection of health-related and other personal data. Laws and regulations in the EU and other jurisdictions apply broadly to the collection, use, storage, disclosure, processing and security of personal data, and have generally become more stringent over time.

For example, the General Data Protection Regulation, or GDPR, imposes strict requirements for processing the personal data of individuals within the EEA. The GDPR allows EU member states to make additional laws and regulations further regulating the processing of genetic, biometric or health data. Failure to comply with the requirements of GDPR and the applicable national data protection laws of the EU member states may result in fines of up to €20 million or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, and other administrative penalties and may expose us to compensation claims from affected individuals.

Further, from January 1, 2021, we are subject to the GDPR and also the UK GDPR, which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, e.g. fines up to the greater of £17.5 million or 4% of the total worldwide annual turnover of the preceding financial year. The European Commission has adopted an adequacy decision in favor of the UK, enabling data transfers from EU member states to the UK without additional safeguards. However, the UK adequacy decision will automatically expire in June 2025 unless the European Commission re-assesses and renews/extends that decision, and it continues to remain under review by the Commission during this period.

Employees

As of December 31, 2022, we had 358 employees, 343 of which are full-time employees. None of our employees is subject to a collective bargaining agreement or represented by a trade or labor union. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees, advisors and consultants. The principal purposes of our equity incentive plans are to attract, retain and reward personnel through the granting of equity-based compensation awards in order to increase shareholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives.

Corporate Information

MeiraGTx Holdings plc was formed on May 1, 2018 under the laws of the Cayman Islands. Our predecessor, MeiraGTx Limited, a limited company under the laws of England and Wales, was formed on March 20, 2015. In connection with our initial public offering ("IPO"), we reorganized whereby MeiraGTx Limited became a wholly owned subsidiary of MeiraGTx Holdings plc.

Available Information

Our website can be found at *http://www.meiragtx.com*. From time to time, we may use our website as a channel of distribution of material company information. Financial and other material information is routinely posted and accessible under the Investors and Media section of our website at *http://www.meiragtx.com*.

We file annual, quarterly and current reports, proxy statements and other information with the U.S. Securities and Exchange Commission ("SEC"). Our SEC filings are available to the public over the Internet at the SEC's website at *http://www.sec.gov*. Our SEC filings are also available without charge under the Investors and Media section of our website at *http://www.meiragtx.com*. We make this information available on our website as soon as reasonably practicable after we electronically file such information with, or furnish it to, the SEC. Our website and the information contained on or connected to that site are not incorporated into this Form 10-K.

ITEM 1A. RISK FACTORS

Investing in our ordinary shares involves a high degree of risk. You should consider carefully the risks described below, together with the other information included or incorporated by reference in this Form 10-K. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our ordinary shares could decline. Other events that we do not currently anticipate or that we currently deem immaterial may also affect our business, prospects, financial condition and results of operations, particularly in light of the continually evolving nature of the COVID-19 pandemic, containment measures, vaccine distribution, vaccination rates, new variants and the related impacts to economic and operating conditions.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception and anticipate that we will incur continued losses for the foreseeable future, and may never achieve or maintain profitability.

We are a clinical stage company with limited operating history. We were formed and began operations in 2015. We have never been profitable and do not expect to be profitable in the foreseeable future. We have incurred net losses since inception, including net losses of approximately $129.6 million and $79.6 million for the twelve months ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of approximately $470.2 million. Since our inception, we have devoted substantially all of our resources to developing our technology platform, establishing our viral vector manufacturing facilities and plasmid and DNA production facility, developing manufacturing processes, advancing the product candidates in our ophthalmology, salivary gland and neurodegenerative disease programs, research and development activities, building our intellectual property portfolio, organizing and staffing our company, developing our business plans, raising capital, securing debt financing and providing general and administrative support for these operations. We have not yet demonstrated an ability to successfully complete large-scale, pivotal clinical trials, obtain marketing approval, manufacture product at a commercial scale, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Given the length of time typically needed to develop a new drug from the time it enters Phase 1 clinical trials to when it is approved for treating patients, predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing genetic medicine products.

We expect to continue to incur significant expenses and additional operating losses for the foreseeable future as we seek to advance product candidates through preclinical and clinical development, expand our research, development and manufacturing activities, develop new product candidates, build and expand our intellectual product portfolio, complete clinical trials, seek regulatory approval and, if we receive regulatory approval, commercialize our products. Furthermore, the costs of advancing product candidates into each succeeding clinical phase tend to increase substantially over time, including the ongoing Phase 3 Lumeos clinical trial of botaretigene sparoparvovec for the treatment of patients with XLRP, although we believe that certain of these increases will be partially offset by the research funding in connection with the Collaboration Agreement. In addition, we expect to continue incurring increasing research and development costs associated with our clinical activities for AAV-hAQP1 for the treatment of radiation-induced xerostomia and xerostomia associated with Sjogren's syndrome, as well as for AAV-GAD for the treatment of Parkinson's disease. The total costs to advance any of our product candidates to marketing approval in even a single jurisdiction would be substantial. Because of the numerous risks and uncertainties associated with gene therapy product development, we are unable to accurately predict the timing or amount of increased expenses or whether we will be able to begin generating revenue from the commercialization of products or achieve or maintain profitability. Our expenses have and will continue to increase substantially as a public company and as we continue to add clinical, scientific, operational, financial, manufacturing, compliance and management information systems and personnel, including personnel to support our product development, manufacturing and planned future commercialization efforts.

Before we generate any revenue from product sales, each of our programs and product candidates will require additional preclinical and/or clinical development, potential regulatory approval in multiple jurisdictions, manufacturing, building of a commercial organization, substantial investment and significant marketing efforts. Our expenses could increase beyond expectations if we are required by the FDA, MHRA, EMA, or other regulatory authorities to perform preclinical studies and clinical trials in addition to those that we currently anticipate. These risks are further described under "—Risks Related to Discovery, Development, Clinical Testing, Manufacturing and Regulatory Approval" and "—Risks Related to Commercialization." As a result, we expect to continue to incur net losses for the foreseeable future. These net losses have had, and will continue to have, an adverse effect on our shareholders' equity and working capital.

As we continue to build our business, we expect our financial condition and operating results may fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any particular quarterly or annual period as indications of future

operating performance. If we are unable to develop and commercialize one or more of our product candidates either alone or with collaborators, or if revenues from any product candidate that receives marketing approval are insufficient, we will not achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability. If we are unable to achieve and then maintain profitability, the value of our equity securities will be adversely affected.

We will require additional capital to fund our operations, which may not be available on acceptable terms, if at all.

We expect to spend substantial amounts to complete the development of, seek regulatory approvals for and commercialize our product candidates, as well as continue to expand our manufacturing and supply chain capabilities. This will require additional capital, which we may raise through equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources. Our ability to raise additional capital when needed has been and may in the future be adversely affected by external factors beyond our control, including changes in the political climate, geopolitical actions, changes in market interest rates, potential reforms and changes to government regulations, the effect of healthcare reform legislation, including those that may limit pricing of pharmaceutical products and drugs, market prices and conditions, prospects for favorable or unfavorable clinical trial results, new product initiatives, the manufacturing and distribution of new products, product safety and efficacy issues, new collaborations, strategic alliances and licensing arrangements, and the COVID-19 outbreak and mitigation measures. Furthermore, we expect to continue to incur costs associated with operating as a public company. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative effect on our financial condition and our ability to pursue our business strategy. In addition, attempting to secure additional financing has diverted and may in the future divert the time and attention of our management from day-to-day activities and harm our product candidate development efforts. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate certain of our research and development programs.

Our operations have consumed significant amounts of cash since inception. As of December 31, 2022, our cash and cash equivalents were $115.5 million. In addition, we expect to receive $21.3 million in receivables which we expect to collect in the first quarter of 2023 from Janssen in connection with the Collaboration Agreement. Based on our cash and cash equivalents at December 31, 2022 and the research funding and milestone payments we expect to receive under the Collaboration Agreement, we estimate that such funds will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2024. This estimate is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Changing circumstances could cause us to spend more than expected or consume capital significantly faster than we currently anticipate, such as inflation or other factors that may significantly increase our business costs. Because the length of time and activities associated with successful development of our product candidates is uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the progress, timing, costs and results of our ongoing clinical development for our X-linked retinitis pigmentosa product candidate, botaretigene sparoparvovec, including the ongoing Phase 3 Lumeos clinical trial of botaretigene sparoparvovec for the treatment of patients with XLRP, for our CNGB3 achromatopsia gene therapy product candidate, AAV-CNGB3, for our CNGA3 achromatopsia gene therapy product candidate, AAV-CNGA3, for our RPE65-associated retinal dystrophy product candidate, AAV-RPE65, and to continue to conduct our ongoing natural history studies for inherited retinal diseases, or IRDs;

- the progress, timing, costs and results of our clinical development for our radiation-induced xerostomia product candidate, AAV-hAQP1, and for our product candidate for the treatment of Parkinson's disease, AAV-GAD;

- the development of our product candidate for the treatment of ALS, AAV-UPF1, for our product candidate for the treatment of xerostomia associated with Sjogren's syndrome, AAV-hAQP1, and our product candidate for the treatment of neovascular age related macular degeneration, or wet AMD;

- the development of potentially transformative gene regulation technology designed to precisely and specifically control gene therapy expression levels via dose-response to orally delivered small molecules;

- continuing our current research programs and our preclinical development of product candidates from our current research programs;

- seeking to identify, assess, acquire and/or develop additional research programs and additional product candidates;

- the preclinical testing and clinical trials for any product candidates we identify and develop;

- the outcome, timing and cost of meeting regulatory requirements established by the FDA, MHRA, EMA and other regulatory authorities;

- the cost of expanding and protecting our intellectual property portfolio, including filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;

- the cost of defending potential intellectual property disputes, including patent infringement actions brought by third parties against us or any of our product candidates;

- the effect of competing technological and market developments;

- the cost of further developing and scaling our manufacturing facilities and processes;

- the cost and timing of completion of commercial-scale manufacturing facilities and activities;

- the cost of making royalty, milestone or other payments under current and any future in-license agreements;

- our ability to establish and maintain strategic collaborations, licensing or other agreements and the financial terms of such agreements;

- the extent to which we in-license or acquire rights to other products, product candidates and technologies;

- the cost of establishing sales, marketing and distribution capabilities for our product candidates in regions where we choose to commercialize our products; and

- the initiation, progress, timing and results of our commercialization of our product candidates, if approved for commercial sale.

Raising additional capital through the sale of equity or convertible debt securities will dilute your ownership interest, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. For example, in connection with entering into the Financing Agreement (as defined below), we issued

warrants to Perceptive (as defined below), to purchase 400,000 ordinary shares at an exercise price of $15.00 per share and 300,000 ordinary shares at an exercise price of $20.00 per share. Additional debt financing or preferred equity financing, if available, may involve agreements that include covenants further limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

We may not have sufficient cash flows or cash on hand to satisfy our debt obligations or covenants under our financing arrangements, or we may not be able to effectively manage our business in compliance with such covenants.

On August 2, 2022, we, as borrower, and our wholly-owned subsidiaries MeiraGTx UK II Limited and MeiraGTx Ireland DAC, as guarantors (the "Subsidiary Guarantors"), entered into a senior secured financing arrangement (the "Financing Agreement") by and among us, the Subsidiary Guarantors, the lenders and other parties from time to time party thereto and Perceptive Credit Holdings III, LP, as administrative agent and lender ("Perceptive"). On December 19, 2022, the Financing Agreement was converted to a note purchase agreement (the "Note Purchase Agreement") between the same parties and under substantially the same terms and conditions as the Financing Agreement, subject to certain customary note constitution terms. The Note Purchase Agreement provides for an initial $75 million notes issuance (the "Tranche 1 Notes"), and we may request an additional $25 million notes issuance to be made at Perceptive's sole discretion before August 2, 2024 (the "Tranche 2 Notes", together with the Tranche 1 Notes, the "Notes"). The Notes incur interest, subject to certain provisions therein, at a fluctuating rate per annum equal to 10.00% plus the secured overnight financing rate administered by the Federal Reserve Bank of New York for a one-month tenor, subject to a 1.00% floor. The Note Purchase Agreement matures on August 2, 2026 and is interest-only during the term. The Note Purchase Agreement also contains various restrictions and covenants, including, among other things, covenants regarding the incurrence of additional indebtedness, limitations on liens, limitations on certain investments, limitations on making distributions, dividends and other payments, mergers, consolidations and acquisitions, dispositions of assets, maintenance of at least $3.0 million in a U.S. bank account, transactions with affiliates, changes to governing documents, changes to certain agreements and leases and changes in control. Our obligations under the Note Purchase Agreement are secured by our London, UK and Shannon, Ireland manufacturing facilities, $3.0 million of our cash and the bank accounts of the Subsidiary Guarantors, and the issued and outstanding equity interests of the Subsidiary Guarantors.

There can be no assurance that Perceptive will elect to issue the Tranche 2 Notes or that our cash and cash equivalents available under the Note Purchase Agreement and under any future financings, together with any funds generated by our operations, will be sufficient to satisfy our debt payment obligations. Our inability to generate funds, obtain financing sufficient to satisfy our debt payment obligations or remain in compliance with the debt covenants may result in such obligations being accelerated by our lenders, which would likely have a material adverse effect on our business, financial condition and results of operations.

The covenants may restrict our current and future operations, particularly our ability to respond to certain changes in our business or industry, or take future actions. Additionally, our ability to comply with these restrictive covenants may be impacted by events beyond our control, such as economic conditions or major central bank policy actions. Our Note Purchase Agreement provides that our breach or failure to satisfy certain covenants constitutes an event of default. Upon the occurrence of an event of default, in addition to an increase in the rate of interest on the Notes of 3% per annum, Perceptive could elect to declare all amounts outstanding thereunder to be immediately due and payable, proceed against the assets we provided as collateral, and, if such debt were accelerated, we may not have sufficient cash on hand or be able to sell sufficient collateral to repay it, which would have an immediate adverse effect on our business and operating results. This could potentially cause us to cease operations and result in a complete loss of your investment in our ordinary shares**.**

We are heavily dependent on the success of our Most Advanced Product Candidates, which are still in development, and if none of them receive regulatory approval or are successfully commercialized, our business may be harmed.

Our future success and ability to generate product revenue is substantially dependent on our ability to successfully develop, obtain regulatory approval for and successfully commercialize our product candidates. We currently have no products that are approved for commercial sale and may never be able to develop marketable products. We have invested and expect to continue to invest a meaningful portion of our efforts and expenditures over the next few years in the development of botaretigene sparoparvovec, AAV-GAD, AAV-CNGB3, AAV-CNGA3, AAV-RPE65 and AAV-hAQP1 (the "Most Advanced Product Candidates"), which will require additional clinical development, management of clinical and manufacturing activities, regulatory approval in multiple jurisdictions, manufacturing sufficient supply, building of a commercial organization, substantial investment and significant marketing efforts before we can generate any revenues from any commercial sales. While we have entered into a Collaboration Agreement with Janssen with respect to AAV-CNGB3, AAV-CNGA3 and botaretigene sparoparvovec, pursuant to which we received a $100 million upfront payment and will also receive funding for certain research, manufacturing, clinical development and commercialization costs, potential additional milestone payments upon the achievement of such milestones and royalties on future net sales of products, there can be no assurance that these three product candidates will be successfully developed and commercialized by us and Janssen. We cannot be certain that our Most Advanced Product Candidates will be successful in clinical trials, receive regulatory approval or be successfully commercialized even if we receive regulatory approval. Even if we receive approval to market our Most Advanced Product Candidates from the FDA, MHRA or other regulatory bodies, we cannot be certain that our product candidates will be successfully commercialized by us or our collaborators, widely accepted in the marketplace or more effective than other commercially available alternatives. Additionally, the research, testing, manufacturing, labeling, approval, sale, marketing and distribution of gene therapy products are and will remain subject to extensive and evolving regulation by the FDA, MHRA and other regulatory authorities. We are not permitted to market our Most Advanced Product Candidates in the United States until they receive approval of a biologics license application, or BLA, from the FDA, we cannot market them in the UK or EU until we receive approval for an MA, from the MHRA or European Commission, respectively, and we cannot market them in other countries until we receive any other required regulatory approval in those countries.

Because some of our other product candidates are based on similar technology as our Most Advanced Product Candidates, if any of our product candidates show unexpected adverse events or a lack of efficacy in the indications we intend to treat, or if we experience other regulatory or developmental issues, our development plans and business could be significantly harmed. Further, competitors may be developing products with similar technology and may experience problems with their products that could identify problems that would potentially harm our business.

We may not be successful in our efforts to identify additional product candidates.

Part of our strategy involves identifying novel product candidates. The process by which we identify product candidates may fail to yield product candidates for clinical development for a number of reasons, including those discussed in these risk factors and also:

- we may not be able to assemble sufficient resources to acquire or discover additional product candidates;
- competitors may develop alternatives that render our potential product candidates obsolete or less attractive;
- potential product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- potential product candidates may, on further study, be shown to have harmful side effects, toxicities or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance;

- potential product candidates may not be effective in treating their targeted diseases;
- the market for a potential product candidate may change so that the continued development of that product candidate is no longer reasonable;
- a potential product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; or
- the regulatory pathway for a potential product candidate may be too complex and difficult to navigate successfully or economically.

In addition, we may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases that may later prove to have greater commercial potential, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights. If we are unable to identify additional suitable product candidates for clinical development, this would adversely impact our business strategy and our financial position and share price and could potentially cause us to cease operations.

Risks Related to Discovery, Development, Clinical Testing, Manufacturing and Regulatory Approval

COVID-19 has impacted and may continue to impact our business, and any other pandemic, epidemic or outbreak of an infectious disease may materially and adversely impact our business, including our preclinical studies, clinical trials, manufacturing capabilities and regulatory approvals.

As a result of the COVID-19 pandemic, we have at times restricted onsite activities and have also experienced some delays in enrolling, treating and monitoring patients in our clinical trials, as well as limited supply chain disruptions. We may experience these or other disruptions from the COVID-19 pandemic or other pandemic, epidemic or outbreak of an infectious disease that could severely impact our business, preclinical studies, clinical trials and laboratory and manufacturing activities, including, for example, delays or difficulties in enrolling patients in our clinical trials, delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff, diversion of healthcare resources away from the conduct of clinical trials, interruption of key clinical trial activities due to limitations on travel imposed or recommended by regulatory authorities or others, interruption or delays in the operations of the FDA, MHRA, EMA or other regulatory authorities, interruption of, or delays in, the manufacturing of our product candidates, interruptions in preclinical studies due to restricted or limited operations at our laboratory facilities, limitations on employee resources that would otherwise be focused on the conduct of our preclinical studies and clinical trials, and interruption or delays to our sourced discovery and clinical activities.

The COVID-19 pandemic continues to impact businesses globally. The extent to which the outbreak or any variants may further impact our business, preclinical studies, clinical trials and laboratory and manufacturing activities will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration of the pandemic, the timing, distribution and effectiveness of vaccines, vaccination rates, travel restrictions and physical distancing requirements in the countries where we do business, business closures or business disruptions, and the effectiveness of actions taken in the countries where we do business to contain and treat the disease, respond to the reduction in global economic activity and resume normal economic and operating conditions. If we or any of the third parties with whom we engage experience prolonged shutdowns or other business disruptions, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively impacted. Furthermore, the magnitude of the economic impact of COVID-19 pandemic and its variants including sustained inflation, supply chain disruptions, and major central bank policy actions continues to be difficult to assess or predict and may continue to result in significant disruption of global financial markets, which could materially affect our performance, financial condition,

results of operations, and cash flows, as well as our ability to raise additional capital. Additionally, major central bank policy actions may have a negative impact on our payment obligations under the Note Purchase Agreement.

It is difficult to predict the time and cost of product candidate development on our novel gene therapy platform. Very few gene therapies have been approved in the United States or in Europe.

We have concentrated a portion of our research and development efforts on our gene therapy platform, which uses both transduction and gene control technology. Our future success depends on the successful development of these novel therapeutic approaches. To date, very few products that utilize gene transfer have been approved in the United States or Europe.

Our gene therapy platform is based on a suite of viral vectors which we can deploy with gene therapy constructs, which relies on the ability of AAV to efficiently transmit a therapeutic gene to certain kinds of cells. The mechanism of action by which these vectors target particular tissues is still not completely understood. Therefore, it is difficult for us to determine that our vectors will be able to properly deliver gene transfer constructs to enough tissue cells to reach therapeutic levels. We cannot be certain that animal models will exist for some of the diseases we expect to pursue, that our viral vectors will be able to meet safety and efficacy levels needed to be therapeutic in humans or that they will not cause significant adverse events or toxicities. Furthermore, prior work conducted by a third party in non-human primates suggests that intravenous, or IV, delivery of certain AAV vectors at very high doses may result in severe toxicity. The indications that we target do not use IV administration for viral vector delivery and do not use doses as high as those tested in these publications, and to date we have not observed the severe toxicities described in these publications with the naturally occurring AAV vectors that we use. However, we cannot be certain that we will be able to avoid triggering toxicities in our future preclinical studies or clinical trials. Any such results could impact our ability to develop a product candidate. As a result of these factors, it is more difficult for us to predict the time and cost of product candidate development, and we cannot predict whether the application of our gene therapy platform, or any similar or competitive gene therapy platforms, will result in the identification, development, and regulatory approval of any product candidates, or that other gene therapy technologies will not be considered better or more attractive. There can be no assurance that any development problems we experience in the future related to our gene therapy platform or any of our research programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. Any of these factors may prevent us from completing our preclinical studies or clinical trials or commercializing any product candidates we may develop on a timely or profitable basis, if at all.

In addition, because our gene regulation technology is still in the research stage, we have not yet been able to assess safety in humans, and there may be long-term effects from treatment that we cannot predict at this time.

Because gene therapy is novel and the regulatory landscape that governs any product candidates we may develop is uncertain and may change, we cannot predict the time and cost of obtaining regulatory approval, if we receive it at all, for any product candidates we may develop.

The regulatory requirements that will govern any novel gene therapy product candidates we develop are not entirely clear and may change. Within the broader genetic medicine field, very few therapeutic products have received marketing authorization from the FDA, MHRA and European Commission. Even with respect to more established products that fit into the categories of gene therapies or cell therapies, the regulatory landscape is still developing. Regulatory requirements governing gene therapy products and cell therapy products have changed frequently and will likely continue to change in the future. Moreover, there is substantial, and sometimes uncoordinated, overlap in those responsible for regulation of existing gene therapy products and cell therapy products, which could impact the timing and cost of any regulatory approval. For example, in the United States, 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 the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical trials are also subject to review and oversight by an institutional biosafety committee, or IBC, and/or

an institutional review board, or IRB, which are local institutional committees or boards, as applicable, that review, approve and oversee basic and clinical research conducted at the institution participating in the clinical trial.

In the EU, the EMA's Committee for Advanced Therapies, or CAT, is responsible for assessing the quality, safety, and efficacy of ATMPs. ATMPs include gene therapy medicines, somatic-cell therapy medicines and tissue-engineered medicines. The role of the CAT is to prepare a draft opinion on an application for marketing authorization for a gene therapy medicinal candidate that is submitted to the EMA. In the EU, the development and evaluation of a gene therapy product must be considered in the context of the relevant EU guidelines. The EMA may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines. As a result, the procedures and standards applied to gene therapy products and cell therapy products may be applied to any gene therapy product candidate we may develop, but that remains uncertain at this point.

Post Brexit, MAAs for ATMPs in Great Britain are regulated nationally and assessed in accordance with the general provisions in place for the licensing of medicines, taking the specific requirements for this group of medicines into account. In Northern Ireland, ATMPs continue to be authorized according to the EU's centralized procedure. Definitions for individual classes of ATMPs remain unchanged and classification of ATMPs are undertaken by the MHRA in accordance with EU legislation and current guidance from CAT. Data, traceability, exemptions from licensing, packaging and post-authorization requirements remain in line with EU requirements transposed into UK law. However, if the EMA issues new guidance on ATMPs going forward, there is a risk of regulatory divergence with the MHRA and separate procedures and standards with which we may need to comply.

Adverse developments in preclinical studies or clinical trials conducted by others in the field of gene therapy and gene regulation products may cause the FDA, MHRA and other regulatory bodies to revise the requirements for approval of any product candidates we may develop or limit the use of products utilizing gene regulation technologies, either of which could harm our business. In addition, the clinical trial requirements of the FDA, MHRA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty, and intended use and market of the potential products. The regulatory approval process for product candidates such as ours can be more expensive and take longer than for other, better known, or more extensively studied pharmaceutical or other product candidates. Further, as we are developing novel treatments for diseases in which there is little clinical experience with new endpoints and methodologies, there is heightened risk that the FDA, MHRA, EMA or other regulatory bodies may not consider the clinical trial endpoints to provide clinically meaningful results, and the resulting clinical data and results may be more difficult to analyze. The prospectively designed natural history studies with the same endpoints as our corresponding clinical trials may not be accepted by the FDA, MHRA, EMA or other regulatory authorities. Regulatory agencies administering existing or future regulations or legislation may not allow production and marketing of products utilizing gene regulation technology in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays, or other impediments to our research programs or the commercialization of resulting products.

The regulatory review committees and advisory groups described above and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional preclinical studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates, or lead to significant post-approval limitations or restrictions. As we advance our research programs and develop future product candidates, we will be required to consult with these regulatory and advisory groups and to comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of any product candidates we identify and develop.

Clinical trials are expensive, time-consuming, difficult to design and implement, and involve an uncertain outcome. Further, we may encounter substantial delays in our clinical trials.

The clinical trials and manufacturing of our product candidates are, and the manufacturing and marketing of our products, if approved, will be, subject to extensive and rigorous review and regulation by numerous government authorities

in the United States and in other countries where we intend to test and market our product candidates. Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. In particular, because our product candidates are subject to regulation as biological drug products, we will need to demonstrate that they are safe, pure, and potent for use in their target indications. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use.

Clinical testing is expensive, can take many years to complete and is subject to uncertainty. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. Failure can occur at any time during the clinical trial process. Even if our future clinical trials are completed as planned, we cannot be certain that their results will support the safety and effectiveness of our product candidates for their targeted indications. Our future clinical trial results may not be successful.

In addition, even if such trials are successfully completed, we cannot guarantee that the FDA, MHRA, EMA or other regulatory authorities will interpret the results as we do, and more trials could be required before we submit our product candidates for approval. To the extent that the results of the trials are not satisfactory to the FDA, MHRA, EMA or other regulatory authorities for support of an MAA, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates.

To date, we have not completed any clinical development programs required for the approval of any of our product candidates. Although we are currently conducting several clinical development programs, we may experience delays in conducting any clinical trials and we do not know whether our ongoing and future clinical trials will begin on time, need to be redesigned, be able to recruit and enroll patients on time or be completed on schedule, or at all. Events that may prevent successful or timely completion of clinical development include:

- inability to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation of clinical trials;
- delays in sufficiently developing, characterizing or controlling a manufacturing process suitable for advanced clinical trials;
- delays in developing suitable assays for screening patients for eligibility for trials with respect to certain product candidates;
- delays in reaching agreement with the FDA, MHRA or other regulatory authorities as to the design or implementation of our clinical trials and obtaining regulatory approval to commence a clinical trial;
- inability to reach an agreement on acceptable terms with clinical trial sites or prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- our inability to recruit and train clinical trial investigators with the appropriate competencies and experience to conduct the clinical trials, administer our product candidates and oversee clinical trial staff;
- delays in obtaining IRB or ethics committee approval or positive opinion at each site;
- inability to recruit suitable patients to participate in a clinical trial;
- inability to develop and validate the companion diagnostic to be used in a clinical trial, if applicable;

- delays in sufficiently developing, designing and manufacturing equipment or medical devices used in our clinical trials;

- patients not completing a clinical trial or returning for post-treatment follow-up;

- clinical sites, CROs, or other third parties deviating from trial protocol or dropping out of a trial;

- failure to perform in accordance with the FDA's good clinical practice, or GCP, requirements, or applicable regulatory guidelines in other countries;

- addressing patient safety concerns that arise during the course of a trial, including occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;

- having an insufficient number of clinical trial sites; or

- inability to manufacture sufficient quantities of our product candidates for use in clinical trials.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates or significantly increase the cost of such trials, including:

- we may experience changes in regulatory requirements or guidance, or receive feedback from regulatory authorities that requires us to modify the design of our clinical trials;

- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon development programs;

- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;

- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

- we or our investigators might have to suspend or terminate clinical trials of our product candidates for various reasons, including non-compliance with regulatory requirements, a finding that our product candidates have undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;

- the cost of clinical trials of our product candidates may be greater than we anticipate, and we may not have funds to cover the costs;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;

- business interruptions resulting from geopolitical actions, including war and terrorism, or a widespread health emergency, such as the COVID-19 pandemic, or natural disasters including earthquakes, typhoons, floods and fires, or from economic or political instability; and

- any future collaborators that conduct clinical trials may face any of the above issues, and they may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- incur unplanned costs;
- be delayed in obtaining marketing approval for our product candidates or not obtain marketing approval at all;
- obtain marketing approval in some countries and not in others;
- obtain marketing approval for indications or patient populations that are not as broad as intended or desired;
- obtain marketing approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA, MHRA or other foreign regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA, MHRA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

Our Most Advanced Product Candidates will require extensive clinical testing before we are prepared to submit a BLA or MAA for regulatory approval. We cannot predict with any certainty if or when we might complete the clinical development for our product candidates and submit a BLA or MAA for regulatory approval of any of our product candidates or whether any such BLA or MAA will be approved. We may also seek feedback from the FDA, MHRA, EMA or other regulatory authorities on our clinical development program, and the FDA, MHRA, EMA or such regulatory authorities may not provide such feedback on a timely basis, or such feedback may not be favorable, which could further delay our development programs.

If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our product candidates could be harmed, and our ability to generate revenues from our product candidates may be delayed. In addition, any delays in our clinical trials could increase our costs, slow down the development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and results of operations. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. The CTR adopted in April 2014 became applicable on January 31, 2022 and repeals the EU Clinical Trials Directive. While the EU Clinical Trials Directive required a separate CTA to be submitted in each member state in which the clinical trial takes place, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application for multi-center trials. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the EU Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said EU Clinical Trials Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR. Compliance with the CTR requirements by us and our third-party service providers, such as CROs, may impact our development plans.

It is currently unclear to what extent the UK will seek to align its regulations with the EU. The UK regulatory framework in relation to clinical trials is derived from existing EU legislation (as implemented into UK law, through secondary legislation). On January 17, 2022, the MHRA launched an eight-week consultation on reframing the UK legislation for clinical trials. The consultation closed on March 14, 2022 and aims to streamline clinical trials approvals, enable innovation, enhance clinical trials transparency, enable greater risk proportionality, and promote patient and public involvement in clinical trials. The outcome of the consultation is being closely watched and will determine whether the UK chooses to align with the CTR or diverge from it to maintain regulatory flexibility. Under the terms of the Protocol on Ireland and Northern Ireland, provisions of the CTR which relate to the manufacture and import of investigational medicinal products and auxiliary medicinal products currently apply in Northern Ireland. On February 27, 2023, the UK Government and the European Commission reached a political agreement on the "Windsor Agreement" which may revise the Protocol on Ireland and Northern Ireland in order to address some of the perceived shortcomings in its operation. If implemented, this may have further impact on the application of the CTR in Northern Ireland. A decision by the UK not to closely align its regulations with the new approach that will be adopted in the EU may have an effect on the cost of conducting clinical trials in the UK as opposed to other countries.

If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may also be impacted.

The affected populations for our product candidates may be smaller than we or third parties currently project, which may affect the addressable markets for our product candidates.

Our projections of the number of people who have the diseases we are seeking to treat, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are estimates based on our knowledge and understanding of these diseases. The total addressable market opportunity for our product candidates will ultimately depend upon a number of factors including the diagnosis and treatment criteria included in the final label, if approved for sale in specified indications, acceptance by the medical community, patient access and product pricing and reimbursement. Incidence and prevalence estimates are frequently based on information and assumptions that are not exact and may not be appropriate, and the methodology is forward-looking and speculative. The process we have used in developing an estimated incidence and prevalence range for the indications we are targeting has involved collating limited data from multiple sources. Accordingly, the incidence and prevalence estimates included, or supporting the information, in our SEC filings and other materials should be viewed with caution. Further, the data and statistical information included, or supporting the information, in our SEC filings and other materials, including estimates derived

from them, may differ from information and estimates made by our competitors or from current or future studies conducted by independent sources.

The use of such data involves risks and uncertainties and is subject to change based on various factors. Our estimates may prove to be incorrect and new studies may change the estimated incidence or prevalence of the diseases we seek to address. The number of patients with the diseases we are targeting in the United States, the UK, the EU and elsewhere may turn out to be lower than expected or may not be otherwise amenable to treatment with our products, or new patients may become increasingly difficult to identify or access, all of which would harm our results of operations and our business.

Negative public opinion of gene therapy and increased regulatory scrutiny of gene therapy and genetic research may adversely impact public perception of our current and future product candidates.

Our potential therapeutic products involve introducing genetic material into patients' cells. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene therapy and gene regulation for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy and gene regulation are unsafe, unethical, or immoral, and, consequently, our products may not gain the acceptance of the public or the medical community. Public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar 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 once approved. For example, in 2003, trials using early versions of murine gamma-retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events, including reported cases of leukemia. Although none of our current product candidates utilize murine gamma-retroviral vectors, our product candidates use a viral delivery system. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates or the halting of clinical trials, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. The risk of cancer remains a concern for gene therapy and we cannot assure that it will not occur in any of our planned or future clinical trials. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. If any such adverse events occur, commercialization of our product candidates or further advancement of our clinical trials could be halted or delayed, which would have a negative impact on our business and operations.

We may fail to maintain the benefits of certain regulatory designations that we have obtained for our product candidates, and may in the future seek and fail to obtain such designations for other of our current or potential future product candidates. Even if such designations are obtained, they may not lead to faster development or regulatory review or approval, and they do not increase the likelihood that our product candidates will receive marketing approval.

A sponsor may seek approval of its product candidate under programs designed to accelerate the FDA's review and approval of new drugs and biological products that meet certain criteria. For example, the FDA has a Fast Track designation program that is intended to expedite or facilitate the process for reviewing new products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. For product candidates with Fast Track designation, sponsors may be eligible for more frequent meetings with the FDA to discuss the

candidate's development plan and more frequent written communication from the FDA about such things as the design of the proposed clinical trials and use of biomarkers. In addition, the FDA may consider for review sections of the BlA on a rolling basis before the complete application is submitted if relevant criteria are satisfied, including an agreement with FDA on the proposed schedule for the submission of portions of the BLA, and the payment of applicable user fees before FDA may initiate a review. Even if Fast Track designation is granted, it may be rescinded if the product no longer meets the qualifying criteria. In April 2018, botaretigene sparoparvovec was issued Fast Track designation by the FDA for the treatment of X-linked retinitis pigmentosa owing to defects in RPGR. In August 2018, AAV-CNGB3 was issued Fast Track designation by the FDA for the treatment of achromatopsia caused by CNGB3 mutations. In January 2021, AAV-CNGA3 was issued Fast Track designation by the FDA for the treatment of achromatopsia caused by CNGA3 mutations.

Similarly, the EMA has established the PRIME scheme to expedite the development and review of product candidates that show a potential to address to a significant extent an unmet medical need, based on early clinical data. In February 2018, AAV-CNGB3 in the treatment of achromatopsia associated with defects in CNGB3 was admitted to the PRIME scheme of the EMA. In February 2020, botaretigene sparoparvovec for the treatment of X-linked retinitis pigmentosa owing to defects in RPGR was admitted to the PRIME scheme of the EMA.

A sponsor may also seek an RMAT designation for its product candidates. In 2017, the FDA established the RMAT designation as part of its implementation of the 21st Century Cures Act. A biological product is eligible for RMAT designation if it qualifies as an RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions, and is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the biological product has the potential to address unmet medical needs for such a disease or condition. In a February 2019 guidance, the FDA also stated that certain gene therapies that lead to a sustained effect on cells or tissues may meet the definition of a regenerative medicine therapy. RMAT designation provides potential benefits that include more frequent meetings with the FDA to discuss the development plan for the product candidate, and eligibility for rolling review and priority review. Products granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites. RMAT-designated products that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real world evidence (such as electronic health records); through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy.

Such regulatory designations are within the discretion of the FDA, MHRA, EMA and other regulatory authorities. Accordingly, even if we believe one of our product candidates meets the criteria for such regulatory programs designed to accelerate the review and approval of new drugs and we seek such designations, the FDA, MHRA, EMA or other applicable regulatory authority may disagree and instead determine not to make such designation for such product candidate. We cannot be sure that our evaluation of our product candidates as qualifying for such regulatory designations will meet the regulatory authority's expectations. In any event, the receipt of such regulatory designations for a product candidate may not result in a faster development process, review, or approval compared to product candidates considered for approval under conventional regulatory procedures and does not assure ultimate approval by the regulatory authorities. In addition, even if additional product candidates are granted such regulatory designations, the regulatory authority may later decide that such product candidates no longer meet the conditions for qualification or decide that the time period for review or approval will not be shortened.

We have received orphan drug designation from the FDA and European Commission for AAV-CNGB3, AAV-CNGA3, AAV-RPE65, botaretigene sparoparvovec, AAV-AIPL1, AAV-RDH12 and from the FDA for AAV-hAQP1, and we may seek orphan drug designation for additional product candidates in the future, but any orphan drug designations we have received or may receive in the future may not confer marketing exclusivity or other expected benefits.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, defined as one occurring in a patient population of fewer than 200,000 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 European Commission grants orphan designation on the basis of the EMA's Committee for Orphan Medicinal Products opinion. A medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment, of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax credits for qualified clinical testing, and user-fee waivers. In addition, if a product receives the first FDA approval of that drug for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same disease or condition for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the rare disease or condition. Under the FDA's regulations, the FDA will deny orphan drug exclusivity to a designated drug upon approval if the FDA has already approved another drug with the same principal molecular structural features, in the case of a biologic, for the same indication, unless the drug is demonstrated to be clinically superior to the previously approved drug. In the EU, orphan designation entitles a party to financial incentives such as reduction of fees or fee waivers, protocol assistance, and access to the centralized MA procedure. Moreover, upon grant of an MA and assuming the requirement for orphan designation are also met at the time the MA is granted, orphan medicinal products are entitled to a ten-year period of market exclusivity for the approved therapeutic indication. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed PIP. This period may be reduced to six years if, at the end of the fifth year, the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity, or where the prevalence of the condition has increased above the orphan designation threshold. In the EU, an MA for an orphan designated product will not be granted if a similar product has been approved in the EU for the same therapeutic indication, unless the applicant can establish that (i) its product, although similar to the orphan medicinal product already authorized is safer, more effective or otherwise clinically superior; (ii) the MA holder for the orphan medicinal product grants its consent; or (iii) if the MA holder of the orphan medicinal product is unable to supply sufficient quantities of product. A similar medicine is a product containing a similar active substance or substances as those contained in an already authorized product. Similar active substance is defined as an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular features) and which acts via the same mechanism.

Post-Brexit, the UK has retained the EU Regulation which governs the designation of medicinal products as orphan medicinal products and which establishes incentives thereto (Regulation (EC) No. 141/2000) as part of UK law by virtue of the EU (Withdrawal) Act 2018. However under the Retained EU Law (Revocation and Reform) Bill, which is currently before the UK Parliament, unless this legislation is expressly preserved and "assimilated" into domestic law or extended by ministerial regulations (to no later than June 23, 2026) it will automatically expire and be revoked by December 31, 2023. There is therefore uncertainty about the future regulations relating to orphan designation in Great Britain, and any future changes to the legal requirements could lead to greater regulatory complexity and increased costs to our business.

The MHRA is responsible for reviewing applications from companies for orphan designation at the time of an MAA. If a medicinal product has been designated orphan in the EU under Regulation (EC) 141/2000, a Great Britain orphan MAA can be made under regulation 50G of the Human Medicines Regulation 2012 (as amended). A UK-wide orphan MAA can only be considered in the absence of an active EU orphan designation. If a UK-wide orphan MA is

granted and the medicinal product subsequently receives EU orphan designation, the MA holder would need to submit a variation to change this to a Great Britain orphan MA.

We have obtained orphan drug designation from the FDA and European Commission for AAV-CNGB3 for the treatment of achromatopsia caused by mutations in the CNGB3 gene, for AAV-CNGA3 for the treatment of achromatopsia due to autosomal-recessive CNGA3 gene mutations, for AAV-RPE65 for the treatment of Leber congenital amaurosis, for botaretigene sparoparvovec for the treatment of X-linked retinitis pigmentosa, for AAV-AIPL1 for the treatment of inherited retinal dystrophy due to defects in AIPL1 gene and for AAV-RDH12 for the treatment of retinol dehydrogenase 12 (RDH12) mutation-associated retinal dystrophy, and we obtained orphan drug designation from the FDA for AAV-hAQP1 for the treatment of grade 2 and grade 3 late xerostomia from parotid gland hypofunction caused by radiotherapy. We may seek orphan drug designation for other current and future product candidates. Even with orphan drug designation, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products, which could prevent us from marketing our product candidates if another company is able to obtain orphan drug exclusivity before we do. In addition, exclusive marketing rights in the United States and the EU may be unavailable if we seek approval for an indication broader than the orphan-designated indication or may be lost in the United States or EU if the FDA or foreign authorities later determine that the request for designation was materially defective or if we are unable to assure sufficient quantities of the drug to meet the needs of patients with the rare disease or condition following approval. Further, even if we obtain orphan drug exclusivity, that exclusivity may not effectively protect our product candidates from competition because different biologics with different active principal molecular structural features can be approved for the same condition. In addition, the FDA can subsequently approve products with the same principal molecular structural features, in the case of a biologic, for the same condition if the FDA concludes that the later product is safer, more effective, or makes a major contribution to patient care. Likewise, in the EU and Great Britain, the European Commission or MHRA, respectively, can authorize a similar product for the same therapeutic indication, if it concludes that the later product is safer, more effective or clinically superior; if the MA holder for the initial orphan medicinal product grants its consent; or if such MA holder is unable to supply sufficient quantities of the product. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, while we intend to seek orphan drug designation for other existing and future product candidates, we may never receive such designations. There have been legal challenges to aspects of the FDA's regulations and policies concerning the exclusivity provisions of the Orphan Drug Act, and future challenges could lead to changes that affect the protections afforded our product candidates in ways that are difficult to predict. It is uncertain how ongoing and future challenges might affect our business.

We and our contract manufacturers for plasmid are subject to significant regulation with respect to manufacturing our products. Our manufacturing facilities and the third-party manufacturing facilities which we rely on 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 plasmid, a component of our viral vectors and product candidates. We completed the fit-out of our first cGMP manufacturing facility in early 2018 and we completed the acquisition of the buildings for our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland in January 2021 to expand our manufacturing and supply chain capabilities. However, if we experience slowdowns or problems with our completed facility or the development and completion of our new facilities and are unable to establish or scale our internal manufacturing capabilities, we will need to continue to contract with manufacturers that can produce the preclinical, clinical and commercial supply of our 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 contract manufacturers for components of our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and

the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. 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 product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA or MAA on a timely basis. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors 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 product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA, MHRA or other regulatory approval of the products will not be granted.

If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could harm our business. If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA, MHRA or other regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be harmed. Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA and/or MAA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, 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 clinical trials may be delayed, or we could lose potential revenue.

Any contamination in our manufacturing process, shortages of raw materials or failure of our plasmid supplier to deliver necessary components, or other issues with the manufacturing process, could result in delays in our clinical development or marketing schedules.

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage. Some of the raw materials required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. In addition, our manufacturing process is complex, and the manufacturing batch cycle period can be several weeks long. Each batch cycle may not yield planned quantities or meet the required standards. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates, failure of manufacturing equipment or systems or other issues with our manufacturing process, 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.

Expanding our manufacturing capacity has and will continue to be costly and we may be unsuccessful in doing so in a timely manner, which could delay our current and future clinical development programs, or delay the commercialization of our product candidates.

In addition to our existing manufacturing facility in London, United Kingdom, we may lease, operate, purchase, or construct additional facilities to conduct expanded manufacturing or other related activities in the future. In January 2021, we completed the acquisition of our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland. Expanding our manufacturing capacity to produce the preclinical, clinical and commercial supply of our products and their components will require completing our new facilities in Ireland, substantial additional expenditures, time, and various regulatory approvals and permits, all of which may be impacted by the COVID-19 pandemic. Further, we will need to hire and train significant numbers of employees and managerial personnel to staff our expanding manufacturing and supply chain operations, including in our new facilities in Ireland. Start-up costs can be large and may exceed our expectations, and scale-up entails significant risks related to process development and manufacturing yields. In addition, we may face difficulties or delays in developing or acquiring the necessary production equipment and technology to manufacture sufficient quantities of our product candidates for use in clinical trials and, should they be approved, to supply the commercial market at reasonable costs and in compliance with applicable regulatory requirements. We may not successfully expand or establish sufficient manufacturing capabilities or manufacture our products economically or in compliance with cGMP and other regulatory requirements, and we and our collaborators may not be able to build or procure additional capacity in the required timeframe to meet the requirements of our clinical programs or to meet potential commercial demand for our product candidates. This could also delay or require us to discontinue one or more of our clinical development programs or could interfere with our efforts to successfully commercialize our products. As a result, our business, prospects, operating results, and financial condition could be materially harmed.

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. The natural history studies may fail to provide us with patients for our clinical trials because patients enrolled in the natural history studies may not be good candidates for our clinical trials or may choose to not enroll in our clinical trials. We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our clinical trials, and even once enrolled we may be unable to retain a sufficient number of patients to complete any of our trials. This may result in increased costs, program delays or both, which could have a harmful effect on our ability to develop our product candidates, or could render further development impossible. The enrollment of patients depends on many factors, including:

- the size and nature of the patient population;
- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to study sites;
- the design of the trial or side effects that may arise in development;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;

- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications we are investigating;

- our ability to obtain and maintain patient consents;

- the risk that patients enrolled in clinical trials will drop out of the trials before completion; and

- business interruptions resulting from geopolitical actions, including war and terrorism, or widespread health emergencies, such as the COVID-19 pandemic, or natural disasters including earthquakes, typhoons, floods and fires, or from economic or political instability.

In addition, other clinical trials for product candidates that are in the same therapeutic areas as our product candidates or approved products for the same clinical indications (such as Luxturna marketed by Spark Therapeutics, Inc. for the treatment of RPE65-associated retinal disease) may reduce the number and type of patients available to us.

Our product candidates may cause serious adverse events or undesirable side effects or have other properties which may delay or prevent their regulatory approval, limit the commercial profile of an approved label, or, result in significant negative consequences following marketing approval, if any.

Serious adverse events or undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, MHRA or other authorities. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects, toxicities or unexpected characteristics, including death. A risk in any gene therapy product based on viral vectors is the risk of insertional mutagenesis.

If unacceptable side effects or deaths arise in the development of our product candidates, we, the FDA, the IRBs at the institutions in which our studies are conducted, DSMB, or other regulatory bodies could suspend or terminate our clinical trials or the FDA, MHRA or other regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Undesirable side effects or deaths in clinical trials with our product candidates may cause the FDA or comparable foreign regulatory authorities to place a clinical hold on the associated clinical trials, to require additional studies, or otherwise to delay or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We expect to have to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may harm our business, financial condition and prospects significantly.

If any of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by any such product, including during any long-term follow-up observation period recommended or required for patients who receive treatment using our products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;

- we may be required to recall a product or change the way such product is administered to patients;

- additional restrictions may be imposed on the marketing of the particular product or the manufacturing processes for the product;
- regulatory authorities may require additional warnings on the label, such as a "black box" warning or contraindication;
- we may be required to implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients or similar risk management measures;
- the product could become less competitive;
- 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 the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Success in preclinical studies or clinical trials may not be indicative of results in future clinical trials.

Results from previous preclinical studies or clinical trials are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. Our product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials.

Success in preclinical testing and early clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate.

Frequently, product candidates that have shown promising results in early clinical trials have subsequently suffered significant setbacks in later clinical trials. In addition, the design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. There is a high failure rate for drugs and biologic products proceeding through clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval, which could negatively impact our business, financial condition, results of operations and prospects.

The regulatory approval processes of the FDA, MHRA, competent authorities in the EU and other regulatory authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA, MHRA, European Commission and other regulatory authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. For instance, the EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. The European Commission's proposal for revision of several legislative instruments related to medicinal products (potentially revising the duration of regulatory exclusivity, eligibility for expedited pathways, etc.) is currently expected during the first quarter of 2023. The proposed revisions,

once they are agreed and adopted by the European Parliament and European Council (not expected before the end of 2024 or early 2025) may have a significant impact on the pharmaceutical industry in the long term.

We have not obtained regulatory approval for any product candidate and it is possible that none of our product candidates in clinical programs or any other product candidates we may seek to develop in the future will ever obtain regulatory approval. Neither we nor any future collaborator is permitted to market any of our product candidates in the United States, the UK or the EU until we receive regulatory approval of a BLA from the FDA or of an MAA from the MHRA or European Commission, respectively. It is possible that the FDA may refuse to accept for substantive review any BLAs, or the MHRA or EMA any of our MAAs, that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates.

Prior to obtaining approval to commercialize a product candidate in the United States, the UK, the EU or elsewhere, we or our collaborators must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the FDA, MHRA, EMA or foreign regulatory agencies, that such product candidates are safe and effective for their intended uses. Results from nonclinical studies and clinical trials can be interpreted in different ways. Even if we believe the nonclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA, MHRA, European Commission or other regulatory authorities. The FDA, MHRA or EMA may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post-approval, or it may object to elements of our clinical development program. Depending on the extent of these or any other FDA, MHRA or EMA required studies, approval of any regulatory approval applications that we submit may be delayed by several years, or may require us to expend significantly more resources than we have available.

Of the large number of potential products in development, only a small percentage successfully complete the FDA, MHRA, or other foreign regulatory approval processes and are commercialized. The lengthy approval process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval to market our product candidates, which would significantly harm our business, results of operations and prospects.

Even if we and / or our collaboration partners, as applicable, obtain FDA, MHRA or European Commission approval for AAV-GAD, botaretigene sparoparvovec, AAV-CNGB3, AAV-CNGA3, AAV-RPE65, AAV-hAQP1 or our other product candidates in the United States, UK or EU, we may never obtain approval for or commercialize them in any other jurisdiction, which would limit our ability to realize their full market potential.

In order to market any products in any particular jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a country-by-country basis regarding safety and efficacy. Approval by the FDA in the United States, the MHRA in Great Britain or the competent authorities in the EU does not ensure approval by regulatory authorities in other countries or jurisdictions. However, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval elsewhere. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country.

Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and increased costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. We do not have any product candidates approved for sale in any jurisdiction, including in international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of any product we develop will be unrealized.

Even if we receive regulatory approval of one or more of our product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense, and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, among other things, will be subject to extensive and ongoing requirements of and review by the FDA, MHRA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, establishment registration and drug listing requirements, continued compliance with cGMP and similar requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and GCP requirements for any clinical trials that we conduct post-approval.

The FDA, MHRA and other regulatory authorities closely regulate the post-approval marketing and promotion of genetic therapy medicines to ensure they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA, MHRA and other regulatory authorities impose stringent restrictions on manufacturers' communications regarding off-label use and if we market our products for uses beyond their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the U.S. federal Food, Drug, and Cosmetic Act, or FDCA, relating to the promotion of prescription drugs may lead to FDA enforcement actions and investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws. Similar risks apply in foreign jurisdictions.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, including adverse events of unanticipated severity or frequency, or with our manufacturing processes or third-party manufacturers, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on manufacturing such products;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or holds on clinical trials;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure or detention; or

- injunctions or the imposition of civil or criminal penalties.

The FDA's and foreign regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We also 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 in other countries. 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 which would adversely affect our business, prospects and ability to achieve or sustain profitability.

Interim, "topline" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or topline data from our clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline and preliminary data also remain subject to audit and verification procedures that may result in the final data being materially different from the topline or preliminary data we previously published. As a result, topline and preliminary data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our clinical trials. Interim data from these trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as subject enrollment continues and more data become available. Adverse differences between interim data and topline, preliminary, or final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our ordinary shares.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to timely capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential

or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Changes in funding for, or disruptions caused by global health concerns impacting, the FDA and other government or regulatory agencies could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products and services from being developed, approved or commercialized in a timely manner, which could negatively impact our business.

The ability of the FDA and foreign regulatory authorities to review and approve new products can be affected by a variety of factors, including government budget and funding levels, disruptions caused by global health concerns such as the COVID-19 pandemic, ability to hire and retain key personnel, including those with experience relating to novel gene therapy product candidates, acceptance of the payment of user fees, statutory, regulatory, and policy changes and other events that may otherwise affect the FDA's or foreign regulatory authorities' ability to perform routine functions. Average review times at the FDA and foreign regulatory authorities have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other government or regulatory agencies such as the EMA, following its relocation to Amsterdam and related reorganization (including staff changes), may also slow the time necessary for new product candidates to be reviewed and/or approved, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Risks Related to Healthcare Laws and Other Legal Compliance Matters

Enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may affect the prices we may set.

In the United States, the UK, the EU and other jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, was enacted, which substantially changed the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA, those of greatest importance to the pharmaceutical and biotechnology industries include the following:

- an annual, non-deductible fee payable by any entity that manufactures or imports certain branded prescription drugs and biologic agents (other than those designated as orphan drugs), which is apportioned among these entities according to their market share in certain government healthcare programs;

- 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;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;

- a licensure framework for follow on biologic products;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

- establishment of a Center for Medicare & Medicaid Innovation at the Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial, Congressional and executive branch challenges to certain aspects of the ACA. On June 17, 2021, the U.S. 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 for purposes of obtaining health insurance coverage through the ACA marketplace from February 15, 2021 through August 15, 2021. 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, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, led to aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022. Under current legislation, the actual reduction in Medicare payment varies from 1% from April 1, 2022 through June 30, 2022, to up to 3% in the final year of this sequester, unless additional action is taken by Congress. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws or any other similar laws introduced in the future may result in additional reductions in Medicare and other health care funding, which could negatively affect our customers and accordingly, our financial operations.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models. In addition, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several U.S. Congressional inquiries and proposed and enacted federal legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, and review the relationship between pricing and manufacturer patient programs. We expect that additional U.S. federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates or put pressure on our product pricing.

In addition, FDA regulations and guidance may be revised or reinterpreted by the FDA in ways that may significantly affect our business and our products. Any new regulations or guidance, or revisions or reinterpretations of existing regulations or guidance, may impose additional costs or lengthen FDA review times for our product candidates. We cannot determine how changes in regulations, statutes, policies, or interpretations when and if issued, enacted or adopted, may affect our business in the future.

Such changes would likely require substantial time and impose significant costs, or could reduce the potential commercial value of our product candidates, and could materially harm our business and our financial results. In addition, delays in receipt of or failure to receive regulatory clearances or approvals for any other products would harm our business, financial condition, and results of operations.

In the UK and EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In addition to continuing pressure on prices and cost containment measures, legislative developments at the UK or the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. The delivery of healthcare in the UK and the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in the UK and in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize our product candidates, if approved.

In markets outside of the United States, the UK and the EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States, the UK the EU or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Our business operations and current and future relationships with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers will be subject to applicable healthcare regulatory laws, which could expose us to penalties.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers, may expose us to broadly applicable fraud and abuse laws and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our product candidates, if approved. Such laws include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or providing any remuneration (including any kickback, bribe, or certain rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. 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;

- the U.S. federal civil and criminal false claims and civil monetary penalties laws, including the civil False Claims Act, which, among other things, impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes which prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the U.S. 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;

- the FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- the U.S. Public Health Service Act, which prohibits, among other things, the introduction into interstate commerce of a biological product unless a biologics license is in effect for that product;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- the U.S. Physician Payments Sunshine Act and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report annually to the government information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiologist assistants and certified nurse midwives), and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

- analogous U.S. state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and state and local laws that require the registration of pharmaceutical sales representatives; and

- similar healthcare laws and regulations in the UK, EU and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, disgorgement, individual imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment, which could affect our ability to operate our business. Further, defending against any such actions can be costly, time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

We are subject to regulation and other legal obligations relating to privacy and data protection. Compliance with these requirements is complex and costly. Failure to comply could materially harm our business.

The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention and security of personal information.

In the U.S., HIPAA imposes privacy, security and breach reporting obligations with respect to individually identifiable health information upon "covered entities" (health plans, health care clearinghouses and certain health care providers), and their respective business associates, individuals or entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity, as well as their covered subcontractors. Most healthcare providers, including research institutions and other vendors from which we may obtain patient health information, are subject to privacy and security regulations promulgated under HIPAA. We do not believe that we are currently acting as a covered entity or business associate under HIPAA and thus are not directly subject to its requirements or penalties. However, depending on the facts and circumstances, we could face substantial criminal penalties if we knowingly receive individually identifiable health information from a HIPAA-covered healthcare provider or research institution that has not satisfied HIPAA's requirements for disclosure of individually identifiable health information.

In addition, certain state laws govern the privacy and security of health information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. Further, we may also be subject to other state laws governing the privacy, processing and protection of personal information. For example, the California Consumer Privacy Act, or CCPA, confers individual privacy rights for California consumers (as such term is defined in the law) and places increased privacy and security obligations on entities handling personal information of consumers or households. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that has increased the likelihood of, and risks associated with, data breach litigation. Further, the California Privacy Rights Act, or the CPRA, generally went into effect in January 2023, and significantly amends the CCPA and imposes additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also created a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. Additional compliance investment and potential business process changes may be required. The CCPA, the CPRA and other domestic privacy and data protection laws and regulations may increase our compliance costs and potential liability.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. For example, the GDPR imposes stringent requirements for processing the personal data of individuals within the European Economic Area, or EEA, which consists of the 27 EU member states plus Norway, Lichtenstein and Iceland. Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to €20 million or up to 4% of the total worldwide annual turnover of the relevant undertaking in the preceding financial year, whichever is higher, and other administrative penalties.

Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the U.S. In July 2020, the Court of Justice of the European Union, or CJEU, limited how organizations could lawfully transfer personal data from the EEA to the U.S. by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions on the use of standard contractual clauses (a standard form of contract approved by the European Commission as an adequate personal data transfer mechanism, and potential alternative to the Privacy Shield), or SCCs. In March 2022, the U.S. and EU announced a new regulatory regime intended to replace the invalidated regulations; however, this new EU-U.S. Data Privacy Framework has not been implemented beyond an executive order signed by President Biden on October 7, 2022 on Enhancing Safeguards for United States Signals Intelligence Activities. European court and regulatory decisions subsequent to the CJEU decision of July 2020 have taken a restrictive approach to international data transfers. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the SCCs cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines. If, owing to the restriction or perceived restriction of personal data transfers, we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results.

Further, we are subject to the UK data protection regime, which imposes separate but similar obligations to those under the GDPR and comparable penalties, including fines of up to £17.5 million or 4% of a noncompliant company's global annual revenue for the preceding financial year, whichever is greater. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

Although we work to comply with applicable laws, regulations and standards, as well as our contractual obligations and other legal obligations, relating to data privacy and security, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction and/or organization to another, and may conflict with one another or other legal obligations with which we must comply. Any failure or perceived failure by us or our employees, representatives, contractors, consultants, collaborators, or other third parties to comply with such requirements or adequately address privacy and security concerns, even if unfounded, could result in additional cost and liability to us, damage our reputation, and adversely affect our business and results of operations.

We are subject to environmental, health and safety laws and regulations, and we may become exposed to liability and substantial expenses in connection with environmental compliance or remediation activities.

Our operations, including our development, testing and manufacturing activities, are subject to numerous environmental, health and safety laws and regulations. These laws and regulations govern, among other things, the controlled use, handling, release and disposal of and the maintenance of a registry for, hazardous materials and biological materials, such as chemical solvents, human cells, carcinogenic compounds, mutagenic compounds and compounds that have a toxic effect on reproduction, laboratory procedures and exposure to blood-borne pathogens. If we fail to comply with such laws and regulations, we could be subject to fines or other sanctions. Additionally, if environmental regulations are enacted that restrict our ability to use one or more of the materials or compounds necessary to manufacture our product candidates, and we are unable to find suitable alternatives or such alternatives require additional testing or will

extend the manufacturing timeline, then we may be unable to manufacture our product candidates in a timely manner, or at all.

We may be subject to environmental liability inherent in our current and historical activities, including liability relating to releases of or exposure to hazardous or biological materials. Environmental, health and safety laws and regulations are becoming more stringent. We may be required to incur substantial expenses in connection with future environmental compliance or remediation activities, in which case, our production efforts or those of our third-party manufacturers may be interrupted or delayed.

Due to our international operations, we are subject to anti-corruption laws, as well as export control laws, customs laws, sanctions laws and other laws governing our operations. If we fail to comply with these laws, we could be subject to civil or criminal penalties, other remedial measures and legal expenses.

Our operations are subject to anti-corruption laws, including the UK Bribery Act 2010, or Bribery Act; the U.S. Foreign Corrupt Practices Act, or FCPA; and other anti-corruption laws that apply in countries where we do business and may do business in the future. The Bribery Act, FCPA, and these other laws generally prohibit us, our officers and our employees and intermediaries from bribing, being bribed by, or providing prohibited payments or anything else of value to government officials or other persons to obtain or retain business or gain some other business advantage. We may in the future operate in jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the Bribery Act, FCPA, or local anti-corruption laws. In addition, we cannot predict the nature, scope, or effect of future regulatory requirements to which any of our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We also are subject to other laws and regulations governing any international operations, including regulations administered by the governments of the UK and the U.S., and authorities in the EU, including applicable export control regulations, economic sanctions on countries and persons, customs requirements and currency exchange regulations, or, collectively, 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. Any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws, or Trade Control laws by UK, U.S., or other authorities, even if it is ultimately determined that we did not violate such laws, could be costly and time-consuming, require significant personnel resources, and harm our reputation.

We have established internal controls to detect and prevent violations of applicable anti-corruption laws and to remedy any weaknesses identified. There can be no assurance, however, that the policies and procedures will be followed at all times or effectively detect and prevent violations of the applicable laws by one or more of our employees, consultants, agents, or collaborators and, as a result, we could be subject to fines, penalties, or prosecution.

Risks Related to Commercialization

We face significant competition in an environment of rapid technological change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer or more advanced or effective than ours, which may harm our financial condition and our ability to successfully market or commercialize any product candidates we may develop.

The development and commercialization of new gene therapy products is highly competitive. Moreover, the gene regulation and manufacturing fields are characterized by rapidly changing technologies and a strong emphasis on intellectual property. We may face competition with respect to any product candidates that we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.

There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we have research programs, including inherited retinal diseases and neurodegenerative diseases. Some of these competitive products and therapies are based on scientific approaches that are similar to our approach, and others are based on entirely different approaches. Differences in the scientific approaches may create confusion or uncertainty among clinical trial investigators or patient populations, which could delay or hinder enrollment or initiation of our clinical trials.

Our platform and products focus on the development of gene therapies and gene regulation technology. In 2017, the FDA approved the first gene treatment for RPE65-associated retinal disease, Luxturna, a commercially available product developed by Spark Therapeutics, Inc., which was purchased by Roche. There are a number of other companies developing ocular gene therapy products, including Applied Genetic Technologies Corporation, and 4D Molecular Therapeutics, Inc. There are a number of companies developing gene therapy products for neurodegenerative diseases, including Voyager Therapeutics, Inc., Brain Neurotherapy Bio, Inc., Axovant Gene Therapies Ltd. and Prevail Therapeutics Inc. (which was purchased by Eli Lilly and Company). In addition to competition from other gene therapies, any products we may develop may also face competition from other types of therapies, such as small molecule, antibody, or protein therapies. Many of our current or potential competitors, either alone or with their collaboration partners, have greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific, manufacturing and management personnel and establishing clinical trial sites and patient enrollment in clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop, limiting demand or the price we are able to charge, or that could render any products that we may develop obsolete or non-competitive. Our competitors also may obtain FDA, MHRA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products.

The successful commercialization of our product candidates will depend in part on the extent to which governmental authorities and health insurers establish coverage, adequate reimbursement levels and pricing policies. Failure to obtain or maintain coverage and adequate reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

The availability of coverage and adequacy of reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford medical services and pharmaceutical products such as our product candidates, assuming FDA approval. Our ability to achieve acceptable levels of coverage and reimbursement for our products or procedures using our products by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize our product candidates. Obtaining coverage and adequate reimbursement for our products may be particularly difficult because of the higher prices often associated with drugs administered under the supervision of a

physician. Separate reimbursement for the product itself or the treatment or procedure in which our product is used may not be available. A decision by a third-party payor not to cover or separately reimburse for our products or procedures using our products, could reduce physician utilization of our products if approved. Assuming there is such coverage by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States, the UK, the EU or elsewhere will be available for our product candidates or any product that we may develop, and any reimbursement that may become available may not be adequate or may be decreased or eliminated in the future.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs or biologics when an equivalent generic drug, biosimilar or a less expensive therapy is available. It is possible that a third-party payor may consider our product candidates as substitutable and only offer to reimburse patients for the less expensive product. Even if we show improved efficacy or improved convenience of administration with our product candidates, pricing of existing third-party therapeutics may limit the amount we will be able to charge for our product candidates. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in our product candidates. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates and may not be able to obtain a satisfactory financial return on our product candidates.

There is significant uncertainty related to the insurance coverage and reimbursement of newly-approved products. In the United States, third-party payors, including private and governmental payors, such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered. The Medicare and Medicaid programs increasingly are used as models in the United States for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs and biologics. Some third-party payors may require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse healthcare providers who use such therapies. We cannot predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases on short notice.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and other countries have and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to fix their own prices for medical products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our product candidates may be reduced compared with the United States and may be insufficient to generate commercially-reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products 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 our product candidates due to the trend toward managed health care, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and biologics and surgical

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

Even if our product candidates receive marketing approval, they may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.

If our product candidates receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If they do not achieve an adequate level of acceptance, we may not generate significant product revenues or become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including but not limited to:

- the efficacy and potential advantages compared to alternative treatments;
- effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- our ability to offer our product candidates for sale at competitive prices;
- the 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 publicity concerning our products or competing products and treatments;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement;
- product labeling or product insert requirements of the FDA, MHRA, EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our product together with other medications.

Because we expect sales of our product candidates, if approved, to generate substantially all of our product revenues for a substantial period, the failure of these product candidates to find market acceptance would harm our business and could require us to seek additional financing.

If we are unable to establish sales, marketing and distribution capabilities either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates or realizing the synergies in the target indications of our programs, even if they are approved.

We do not have any infrastructure for the sales, marketing or distribution of our products, and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so or we may seek collaborative arrangements or external funding to commercialize our product candidates. For example, Janssen will be solely responsible for the commercialization of botaretigene sparoparvovec, AAV-CNGB3 and AAV-CNGA3 pursuant

to our Collaboration Agreement with them. There are significant expenses and risks involved with establishing our own sales, marketing and distribution capabilities, including our ability to hire, retain and appropriately incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of such capabilities could delay any product launch, which would adversely impact the commercialization of our product candidates. Additionally, if any commercial launch is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

We may not have the resources in the foreseeable future to allocate to the sales and marketing of our product candidates in certain markets. Therefore, our future sales in these markets will largely depend on our ability to enter into and maintain collaborative relationships for such capabilities, the collaborator's strategic interest in the product and such collaborator's ability to successfully market and sell the product. We may pursue collaborative arrangements regarding the sale and marketing of AAV-GAD, AAV-RPE65, AAV-hAQP1 or other future gene therapy programs, if approved, for the United States and/or certain markets overseas; however, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or if able to do so, that they will have effective sales forces.

If we are unable to build our own sales force or negotiate or maintain a collaborative relationship for the commercialization of our product candidates, we may be forced to delay potential commercialization or reduce the scope of our sales or marketing activities. If we elect to increase our expenditures to fund commercialization activities internationally, we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. We could enter into arrangements with collaborative partners at an earlier stage than otherwise would be ideal and we may be required to relinquish rights or otherwise agree to terms unfavorable to us, any of which may have an adverse effect on our business, operating results and prospects.

Some indications targeted by our ophthalmology programs are rare, but we anticipate realizing synergies in commercializing our IRD product candidates, should they be approved. Failure to realize synergies in our sales, marketing and distribution efforts may harm our commercialization efforts.

If we or our collaborators are unable to establish or maintain adequate sales, marketing and distribution capabilities, we will not be successful in commercializing our product candidates and may not become profitable and may incur significant additional losses. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If any of our products are commercialized outside of the United States, the UK or the EU, a variety of risks associated with international operations could adversely affect our business.

If any of our products are approved for commercialization, we have entered into, and intend to enter into, agreements with third parties to market them in certain jurisdictions outside the United States, the UK and the EU, such as under our Collaboration Agreement with Janssen. We expect that we and our third-party collaborators will be subject to additional risks related to international pharmaceutical operations, including:

- different regulatory requirements for drug and biologic approvals and rules governing drug and biologic commercialization in foreign countries;
- tighter restrictions on privacy and the collection and use of patient data;
- reduced or loss of protection for intellectual property rights;
- foreign reimbursement, pricing and insurance regimes;

- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- business interruptions resulting from geopolitical actions, including war and terrorism, or widespread health emergencies, such as the COVID-19 pandemic, or natural disasters including earthquakes, typhoons, floods and fires, or from economic or political instability;
- greater difficulty with enforcing our contracts;
- potential noncompliance with the FCPA, the Bribery Act and similar anti-bribery and anticorruption laws in other jurisdictions;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- workforce uncertainty in countries where labor unrest is more common than in the United States and compliance with tax, employment, immigration and labor laws for employees living or traveling abroad.

We have no prior experience in these areas and we may rely on other third parties to help us establish our international commercialization operations. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by individual countries in Europe with which we and our third-party collaborators will need to comply. If we are unable to successfully manage the challenges of international expansion and operations, our business and operating results could be harmed.

Any product candidates for which we intend to seek approval as biologic products may face competition sooner than anticipated.

The ACA includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed by the FDA. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own pre-clinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of the other company's product.

We believe that any of our product candidates approved as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that any of our product candidates approved as a biological product under a BLA would not qualify for the 12-year period of exclusivity or that this exclusivity could be shortened due to Congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Jurisdictions outside the United States have established abbreviated pathways for regulatory approval

of biological products that are biosimilar to earlier approved reference products. For example, the EU has had an established regulatory pathway for biosimilars since 2006. Moreover, the extent to which a biosimilar, once licensed, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences.

Risks Related to Our Dependence on Third Parties

If our cGMP and GMP manufacturing facilities are unable to supply our product candidates for all of our current preclinical, clinical and potential commercial needs, we will be forced to seek out third-party manufacturers. We currently contract with third parties for the manufacture of plasmid used in producing our product candidates. Relying on third parties increases the risk that we will not have sufficient quantities of such materials, product candidates, or any medicines that we may develop and commercialize, or that such supply will not be available to us at an acceptable cost, which could delay, prevent, or impair our development or commercialization efforts.

We produce our product candidates in our cGMP viral vector manufacturing facility completed in early 2018 and we completed the acquisition of our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland in January 2021 to expand our manufacturing and supply chain capabilities. However, if our current facility is damaged, suffers any form of delay or regulatory challenges, we experience slowdowns or problems with the development and completion of our new facilities or we are unable to scale our internal manufacturing capabilities to meet demand for our product candidates, we will need to contract with third-party manufacturers to produce our product candidates. While we now have our own plasmid manufacturing capabilities in our Shannon, Ireland facilities, we may also rely on third-party manufacturers from time to time for the manufacture of plasmid used in the production of some of our product candidates. We do not have a long-term supply agreement with any of the third-party manufacturers, and we purchase our required supply on a purchase order basis.

We and our third-party manufacturers may also encounter difficulties or delays in manufacturing of our product candidates or the plasmid used in the production of our product candidates. Geopolitical actions, natural disaster or a widespread health emergency, such as the COVID-19 pandemic, could impact our supply chain. To the extent that we or our third-party manufacturers are located in geographies affected by these matters, it may result in the temporary closing of manufacturing facilities and may increase the costs associated with manufacturing our product candidates.

We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the possible breach of the manufacturing agreement by the third party, including failure to provide appropriate quantities in a timely manner;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and
- reliance on the third party for regulatory compliance, quality assurance, safety, and pharmacovigilance and related reporting.

We and our third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements that might be required by the FDA, MHRA or EMA. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines,

injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocations, seizures or recalls of product candidates or medicines, operating restrictions, and criminal prosecutions, any of which could adversely affect supplies of our candidates and harm our business, financial condition, results of operations, and prospects.

Any therapies that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP or similar regulations and that might be capable of manufacturing for us. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval.

Our current and anticipated future dependence upon others for the manufacture of any product candidates we may develop or any components required for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

We have in the past, and may in the future, collaborate with third parties for the development, manufacture and commercialization of our product candidates. We may not succeed in establishing and maintaining collaborative relationships, which may significantly limit our ability to develop and commercialize our product candidates successfully, if at all.

We have entered into collaboration agreements with third parties for the development and commercialization of our product candidates, including our Collaboration Agreement with Janssen for the development and commercialization of AAV-CNGB3, AAV-CNGA3 and botaretigene sparoparvovec. We have also entered into a manufacturing research collaboration agreement with Janssen to further develop processes for manufacturing AAV viral vectors. We may seek additional collaborative relationships in the future. Failure to obtain a collaborative relationship for our product candidates may significantly impair their commercial potential. We also may need to enter into collaborative relationships to provide funding to support our other research and development programs. The process of establishing and maintaining collaborative relationships is difficult, time-consuming and involves significant uncertainty, such as:

- a collaboration partner may shift its priorities and resources away from our product candidates due to a change in business strategies, or a merger, acquisition, sale or downsizing;
- a collaboration partner may seek to renegotiate or terminate their relationships with us due to unsatisfactory clinical results, manufacturing issues, a change in business strategy, a change of control or other reasons;
- a collaboration partner may cease development in therapeutic areas which are the subject of our strategic collaboration;
- a collaboration partner may not devote sufficient capital or resources towards our product candidates;
- a collaboration partner may change the success criteria for a product candidate thereby delaying or ceasing development of such candidate;
- a significant delay in initiation of certain development activities by a collaboration partner will also delay payment of milestones tied to such activities, thereby impacting our ability to fund our own activities;
- a collaboration partner could develop a product that competes, either directly or indirectly, with our product candidate;

- a collaboration partner with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of a product;
- a collaboration partner with manufacturing responsibilities may encounter regulatory, resource or quality issues and be unable to meet demand requirements;
- a collaboration partner may terminate a strategic alliance;
- a dispute may arise between us and a partner concerning the research, development or commercialization of a product candidate resulting in a delay in milestones, royalty payments or termination of an alliance and possibly resulting in costly litigation or arbitration which may divert management attention and resources; and
- a partner may use our products or technology in such a way as to make us subject to litigation with a third party.

If any collaborator fails to fulfill its responsibilities in a timely manner, or at all, our research, clinical development, manufacturing or commercialization efforts related to that collaboration could be delayed or terminated, or it may be necessary for us to assume responsibility for expenses or activities that would otherwise have been the responsibility of our collaborator. If we are unable to establish and maintain collaborative relationships on acceptable terms or to successfully transition terminated collaborative agreements, we may have to delay or discontinue further development of one or more of our product candidates, undertake development and commercialization activities at our own expense or find alternative sources of capital.

We have relied, and we expect to continue to rely, on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if these third parties perform in an unsatisfactory manner, our business could be harmed.

We expect to rely on CROs, clinical trial sites, and other vendors to ensure our preclinical studies and clinical trials are conducted properly and on time. We may also engage third parties such as clinical data management organizations, medical institutions and clinical investigators to conduct or assist in our clinical trials or other preclinical and clinical research and development work. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our third-party service providers' activities. Nevertheless, we will be responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol, legal, quality, regulatory and scientific standards. Our reliance on these third parties does not relieve us of our regulatory responsibilities. For example, we are conducting the Phase 3 Lumeos clinical trial of botaretigene sparoparvovec for the treatment of patients with XLRP caused by mutations in the RPGR gene at multiple clinical trial sites in North America and Europe. If any locations terminate the clinical trial, we may be required to find another party to conduct any new trials. We may be unable to find a new party to conduct new trials of our product candidates or obtain clinical supply of our product candidates or AAV vectors for such trials. If we elect to internalize some or all activities related to the conduct of our preclinical studies or clinical trials that are currently performed by our third-party service providers, or if we are required to do so due to a service provider's termination of our relationship, then we may be required to source additional technology and personnel in order to perform the relevant activities. We may be unsuccessful in our efforts to internalize some or all relevant activities, either on the desired timeline or at all.

Our third-party service providers are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time, attention, expertise and resources to our clinical and nonclinical programs. These third-party service providers may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our third-party service providers do not successfully carry out their contractual duties or obligations or fail to meet

expected deadlines, or if the quality or accuracy of the preclinical or clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our preclinical studies or clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates could be harmed, our costs could increase, and our ability to generate revenues could be delayed.

If our relationship with any CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we intend to carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have an adverse impact on our business, financial condition and prospects.

Risks Related to Intellectual Property

We depend on proprietary technology licensed from others. If we lose our existing licenses or are unable to acquire or license additional proprietary rights from third parties, we may not be able to continue developing our product candidates.

We currently in-license certain intellectual property from research institutions, universities and other third parties. We may also enter into additional agreements, including license agreements, with other parties in the future that impose diligence, development and commercialization timelines, milestone payments, royalties, insurance and other obligations on us. If we fail to comply with our obligations to any of our current or future collaborators, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product candidate that is covered by these agreements, which could adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

We may rely on other third parties from whom we license proprietary technology to file and prosecute patent applications and maintain patents and otherwise protect the intellectual property we license from them. We may have limited control over these activities or any other intellectual property that may be related to our in-licensed intellectual property. For example, we cannot be certain that such activities by these licensors will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents and other intellectual property rights. We may have limited control over the manner in which our licensors initiate an infringement proceeding against a third-party infringer of the intellectual property rights, or defend certain of the intellectual property that may be licensed to us. It is possible that the licensors' infringement proceedings or defense activities may be less vigorous than if we conduct them ourselves. The licensing and acquisition of third-party intellectual property rights is a competitive practice, and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire. If we are unable to obtain and maintain patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

If we are unable to obtain and maintain patent protection for our technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our proprietary technologies, product candidate development programs and product candidates. Our success depends in part on our ability to secure and maintain patent protection in the United States and other countries with respect to our current product candidates and any future product candidates we may develop. We seek to protect our proprietary position by filing or collaborating with our licensors to file patent applications in the United States and abroad related to our proprietary technologies, development programs and product candidates. The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Moreover, the issuance, scope, validity, enforceability and commercial value of our patent rights are uncertain.

It is also possible that we might fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We may not have the right to control the preparation, filing, and prosecution of patent applications, or to maintain the rights to patents licensed to third parties. Therefore, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our proprietary products and technology, including current product candidates, any future product candidates we may develop, and our gene regulation technology in the United States or in other countries, in whole or in part. Alternately, our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technologies. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which can prevent a patent from issuing from a pending patent application or later invalidate or narrow the scope of an issued patent. For example, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. In addition, obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements. Even if patents do successfully issue and even if such patents cover our current product candidates, any future product candidates we may develop and our gene regulation technology, third parties may challenge their validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated, or held unenforceable. Any successful challenge to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any of our product candidates or gene regulation technology. Our competitors may be able to circumvent our patents by developing similar or alternative product candidates in a non-infringing manner. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate and our gene regulation technology under patent protection could be reduced.

If the patent applications we hold or have in-licensed with respect to our development programs and product candidates fail to issue, if their validity, breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for any of our current or future product candidates or technology, it could dissuade companies from collaborating with us to develop product candidates, encourage competitors to develop competing products or technologies and threaten our ability to commercialize future product candidates. Any such outcome could harm our business.

The patent position of biotechnology and pharmaceutical companies is uncertain, involves complex legal and factual questions, and is characterized by the existence of large numbers of patents and frequent litigation based on allegations of patent or other intellectual property infringement or violation. In addition, the laws of jurisdictions outside

the United States may not protect our rights to the same extent as the laws of the United States. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Thus, even if our patent applications issue as patents, they may not issue in a form that will provide us with meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Moreover, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Without patent protection for our current or future product candidates, we may be open to competition from generic versions of such 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 similar or identical to ours.

Third parties may assert claims against us alleging infringement of their patents and proprietary rights, or we may need to become involved in lawsuits to defend or enforce our patents, either of which could result in substantial costs or loss of productivity, delay or prevent the development and commercialization of our product candidates, prohibit our use of proprietary technology or sale of products or put our patents and other proprietary rights at risk.

Our commercial success depends, in part, upon our ability to develop, manufacture, market and sell our product candidates without alleged or actual infringement, misappropriation or other violation of the patents and proprietary rights of third parties. However, our research, development and commercialization activities may be subject to claims that we infringe or otherwise violate patents or other intellectual property rights owned or controlled by third parties. Litigation relating to infringement or misappropriation of patent and other intellectual property rights in the pharmaceutical and biotechnology industries is common, including patent infringement lawsuits, interferences, oppositions and *inter partes* reviews, and reexamination proceedings before the U.S. Patent and Trademark Office, or USPTO, and corresponding foreign patent offices. In addition, many companies in intellectual property-dependent industries, including the biotechnology and pharmaceutical industries, have employed intellectual property litigation as a means to gain an advantage over their competitors. Numerous U.S., EU and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates, and as the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the intellectual property rights of third parties. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us.

We may be subject to third-party claims including infringement, interference or derivation proceedings, post-grant review and *inter partes* review before the USPTO or similar adversarial proceedings or litigation in other jurisdictions. Even if such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, and the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents, and the holders of any such patents may be able to prohibit our use of those compositions, formulations, methods of treatment, prevention or use or other technologies, effectively blocking our ability to develop and commercialize the applicable product candidate until such patent expires or is finally determined to be invalid or unenforceable or unless we obtained a license.

In addition, defending such claims would cause us to incur substantial expenses and, if we are not successful in defending such claims, it could cause us to pay substantial damages if we are found to be infringing a third party's patent rights. These damages potentially include increased damages (possibly treble damages) and attorneys' fees if we are found to have infringed such rights willfully. Further, if a patent infringement suit is brought against us or our third-party service providers, our development, manufacturing or sales activities relating to the product or product candidate that is the subject of the suit may be delayed or terminated. As a result of patent infringement claims, or in order to avoid potential infringement claims, we may choose to seek, or be required to seek, a license from the third party, which may require payment of substantial royalties or fees, or require us to grant a cross-license under our intellectual property rights. These licenses may not be available on reasonable terms or at all. Even if a license can be obtained on reasonable terms, the rights may be nonexclusive, which would give our competitors access to the same intellectual property rights. If we are unable to enter into a license on acceptable terms, we could be prevented from commercializing one or more of our product candidates, or forced to modify such product candidates, or to cease some aspect of our business operations, which could harm our business significantly. We might also be forced to redesign or modify our product candidates so that we no longer infringe the third-party intellectual property rights, which may result in significant cost or delay to us, or which redesign or modification could be impossible or technically infeasible. Even if we were ultimately to prevail, any of these events could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

Competitors may infringe our patents or other intellectual property. If we or one of our licensors were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid or unenforceable. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, 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 this type of litigation. Such litigation or proceedings could substantially increase our operating losses and reduce our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have an adverse effect on our ability to compete in the marketplace.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent, which might adversely affect our ability to develop, manufacture and market our product candidates.

We cannot guarantee that any of our or our licensors' patent searches or analyses, including but not limited to the identification of relevant patents, analysis of the scope of relevant patent claims or determination of the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States, the UK, the EU and elsewhere that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. For example, in the United States, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States, the UK, the EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our product candidates could be filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. After issuance, the scope of patent claims remains subject to construction as determined by an interpretation

of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that our product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States, the UK, the EU or elsewhere that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

If we fail to correctly identify or interpret relevant patents, we may be subject to infringement claims. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay monetary damages, we may be temporarily or permanently prohibited from commercializing our product candidates. We might, if possible, also be forced to redesign our product candidates in a manner that no longer infringes third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

Obtaining and enforcing patents in the biotechnology and genetic medicine industries involve both technological complexity and legal complexity. In addition, the Leahy-Smith America Invents Act, or the AIA, which was passed in September 2011, resulted in significant changes to the U.S. patent system.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned from a "first-to-invent" to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. 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 a patent on the invention regardless of whether another inventor had made the invention earlier. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we made the invention before it was made by the third party. This will require us to be cognizant of the time from invention to filing of a patent application and diligent in filing patent applications, but circumstances could prevent us from promptly filing patent applications on our inventions.

In addition, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim. An adverse determination in any such proceeding could reduce the scope of, or invalidate, our owned or in-licensed patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Additionally, the U.S. Supreme Court has ruled on several patent cases in recent years either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations, and there are other open questions under patent law that courts have yet to decisively address. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways and could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. In addition, the European patent system is relatively stringent in the type of amendments that are allowed during prosecution, but, the

complexity and uncertainty of European patent laws has also increased in recent years. Complying with these laws and regulations could limit our ability to obtain new patents that may be important for our business.

We enjoy only limited geographical protection with respect to certain patents and we may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents covering our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In-licensing patents covering our product candidates in all countries throughout the world may similarly be prohibitively expensive, if such opportunities are available at all. And in-licensing or filing, prosecuting and defending patents even in only those jurisdictions in which we develop or commercialize our product candidates may be prohibitively expensive or impractical. Competitors may use our and our licensors' technologies in jurisdictions where we have not obtained patent protection or licensed patents to develop their own products and, further, may export otherwise infringing products to territories where we and our licensors have patent protection, but enforcement is not as strong as that in the United States, the UK or the EU. These products may compete with our product candidates, and our or our licensors' patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws or regulations in the United States, the UK and the EU, and many companies have encountered significant difficulties in protecting and defending proprietary rights in such jurisdictions. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets or other forms of intellectual property, which could make it difficult for us to prevent competitors in some jurisdictions from marketing competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, are likely to result in substantial costs and divert our efforts and attention from other aspects of our business, and additionally could put at risk our or our licensors' patents of being invalidated or interpreted narrowly, could increase the risk of our or our licensors' patent applications not issuing, or could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, while damages or other remedies may be awarded to the adverse party, which may be commercially significant. If we prevail, damages or other remedies awarded to us, if any, may not be commercially meaningful. Accordingly, our efforts, or the efforts of our licensors or collaborators, to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

The term of any individual patent depends on applicable law in the country where the patent is granted. In the United States, provided all maintenance fees are timely paid, a patent generally has a term of 20 years from its application filing date or earliest claimed non-provisional filing date. Extensions may be available under certain circumstances, but the life of a patent and, correspondingly, the protection it affords is limited. Even if we or our licensors obtain patents covering our product candidates, when the terms of all patents covering a product expire, our business may become subject to competition from competitive medications, including generic medications. Given the amount of time required for the development, testing and regulatory review and approval of new product candidates, patents protecting such candidates may 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 similar or identical to ours.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of marketing exclusivity for our product candidates, our business may be harmed.

In the United States, a patent that covers an FDA-approved drug or biologic may be eligible for a term extension designed to restore the period of the patent term that is lost during the premarket regulatory review process conducted by the FDA. Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, which permits a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. In the UK and the EU, our product candidates may be eligible for term extensions based on similar legislation. In each of these jurisdictions, however, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Even if we are granted such extension, the duration of such extension may be less than our request. If we are unable to obtain a patent term extension, or if the term of any such extension is less than our request, the period during which we can enforce our patent rights for that product will be essentially shortened and our competitors may obtain approval to market competing products sooner. The resulting reduction in revenue from applicable products could be substantial.

Our proprietary rights may not adequately protect our technologies and product candidates, and do not necessarily address all potential threats to our competitive advantage.

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

- others may be able to make products that are the same as or similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed;
- others, including inventors or developers of our owned or in-licensed patented technologies who may become involved with competitors, may independently develop similar technologies that function as alternatives or replacements for any of our technologies without infringing our intellectual property rights;
- we or our licensors or our other collaboration partners might not have been the first to conceive and reduce to practice the inventions covered by the patents or patent applications that we own, license or will own or license;
- we or our licensors or our other collaboration partners might not have been the first to file patent applications covering certain of the patents or patent applications that we or they own or have obtained a license, or will own or will have obtained a license;
- we or our licensors may fail to meet obligations to the U.S. government with respect to in-licensed patents and patent applications funded by U.S. government grants, leading to the loss of patent rights;
- issued patents that we own or exclusively license may not provide us with any competitive advantage, or may be held invalid or unenforceable, as a result of legal challenges by our competitors; and
- our competitors might conduct research and development activities in countries where we do not have patent rights, or in countries where research and development safe harbor laws exist, and then use the

information learned from such activities to develop competitive products for sale in our major commercial markets.

Our reliance on third parties may require us to share our trade secrets, which increases the possibility that our trade secrets will be misappropriated or disclosed, and confidentiality agreements with employees and third parties may not adequately prevent disclosure of trade secrets and protect other proprietary information.

We consider proprietary trade secrets, confidential know-how and unpatented know-how to be important to our business. We may rely on trade secrets and confidential know-how to protect our technology, especially where patent protection is believed by us to be of limited value. However, trade secrets and confidential know-how are difficult to protect, and we have limited control over the protection of trade secrets and confidential know-how used by our licensors, collaborators and suppliers. Because we have relied in the past on third parties to manufacture our product candidates, because we may continue to do so in the future, and because we expect to collaborate with third parties on the development of our current product candidates and any future product candidates we develop, we may, at times, share trade secrets with them. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Under such circumstances, trade secrets and confidential know-how can be difficult to maintain as confidential.

To protect this type of information against disclosure or appropriation by competitors, our policy is to require our employees, consultants, contractors and advisors to enter into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with us 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, including our trade secrets. However, current or former employees, consultants, contractors and advisers may unintentionally or willfully disclose our confidential information to competitors, and confidentiality agreements may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. We may also be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of their former employers or other 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 competitive 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 an adverse effect on our business and results of operations. Enforcing a claim that a third party obtained illegally and is using trade secrets and/or confidential know-how is expensive, time consuming and unpredictable, and the enforceability of confidentiality agreements may vary from jurisdiction to jurisdiction. Courts outside the United States are sometimes less willing to protect proprietary information, technology and know-how.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected. Our trademark MeiraGTx has been registered in the EU, UK and United States. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our unregistered trademarks or trade names. Over the long term, if we are unable to successfully register our trademarks and trade names and establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could

result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

We may need to license or acquire additional intellectual property from third parties, and such intellectual property may not be available or may not be available on commercially reasonable terms.

The growth of our business may depend in part on our ability to acquire or in-license additional proprietary rights. For example, our programs may involve product candidates or equipment that may require the use of additional proprietary rights held by third parties. Our product candidates may also require specific formulations to work effectively and efficiently. These formulations may be covered by intellectual property rights held by others. We may develop products containing our compositions and pre-existing pharmaceutical compositions. These pharmaceutical products may be covered by intellectual property rights held by others. We may be required by the FDA, MHRA, EMA or other foreign regulatory authorities to provide a companion diagnostic test or tests with our product candidates. These diagnostic test or tests may be covered by intellectual property rights held by others. We may be unable to acquire or in-license any relevant third-party intellectual property rights that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compositions or methods covered by such third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on such intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license under such intellectual property rights, any such license may be non-exclusive, which may allow our competitors access to the same technologies licensed to us.

Risks Related to Employee Matters and Managing Growth

We may need to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2022, we had 358 employees. We expect to continue to expand our organization, including hiring and training employees and managerial personnel to staff our expanding manufacturing and supply chain operations in our new facilities in Ireland. We may have difficulty identifying, hiring and integrating new personnel. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our expected growth, our expenses may increase more than expected, our potential ability to generate revenue could be reduced and we may not be able to implement our business strategy. Many of the biotechnology companies that we compete against for qualified personnel and consultants have greater financial and other resources, different risk profiles and a longer history in the industry than we do. If we are unable to continue to attract and retain high-quality personnel and consultants, the rate and success at which we can discover and develop product candidates and operate our business will be limited.

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

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the development, regulatory, commercialization and business development expertise of Alexandria Forbes, Ph.D., our President and Chief Executive Officer, Rich Giroux, our Chief Operating Officer and Chief Financial Officer and Stuart Naylor, Ph.D., our Chief Development Officer, as well as the other principal members of our management, scientific and clinical teams. Although we have formal employment agreements with certain of our executive officers, these agreements do not prevent them from terminating their employment with us at any time and, for certain of our executive officers, entitle them to receive severance payments in connection with their voluntary resignation of employment.

If we lose one or more of our executive officers or key employees, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize product candidates successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be engaged by entities other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to develop and commercialize product candidates will be limited.

Potential product liability lawsuits against us could cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

The use of our product candidates in clinical trials and the sale of 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, health care providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. On occasion, large judgments have been awarded in class action lawsuits based on products that had unanticipated adverse effects. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation and significant negative media attention;
- withdrawal of participants from our clinical trials;
- significant time, costs and diversion of management resources to defend the related litigation;
- substantial monetary awards to patients or other claimants;
- inability to commercialize our product candidates;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- decreased demand for our product candidates, if approved for commercial sale; and
- loss of revenue.

Our insurance policies are expensive and protect us only from some business risks, which leaves us exposed to significant uninsured liabilities.

We do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, clinical trial liability, employment practices liability, property, auto, workers' compensation, umbrella, cyber and directors' and officers' insurance. Any additional product liability insurance coverage we acquire in the future, may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and restrictive, and in the future 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. If we obtain marketing approval for our product candidates, we intend to acquire insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. A successful product liability claim or series of claims brought against us could cause our share price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business, including preventing or limiting the commercialization of any product candidates we develop. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

Operating as a public company may make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, our board committees or as executive officers. If we are unable to maintain existing insurance with adequate levels of coverage, any significant uninsured liability may require us to pay substantial amounts, which would adversely affect our cash position and results of operations.

Our employees and independent contractors, including consultants, vendors, and any third parties we may engage in connection with development and commercialization may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could harm our business.

Misconduct by our employees and independent contractors, including consultants, vendors, and any third parties we may engage in connection with development and commercialization, could include intentional, reckless or negligent conduct or unauthorized activities that violate: (i) applicable laws and regulations of the FDA, MHRA, EMA and other regulatory or governmental authorities, including those laws that require the reporting of true, complete and accurate information to such authorities; (ii) manufacturing standards; (iii) data privacy, security, fraud and abuse and other healthcare laws and regulations; or (iv) laws that require the reporting of true, complete and accurate financial information and data. Specifically, 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. Activities subject to these laws could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creation of fraudulent data in preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. 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 such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. 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 and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid, other U.S. federal healthcare programs or healthcare programs in other jurisdictions, integrity oversight and

reporting obligations to resolve allegations of non-compliance, individual imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

Our business and operations may suffer in the event of system failures and our systems and those of our business partners and service providers may be vulnerable to cybersecurity risks.

Our information technology systems, including manufacturing systems, as well as those of our business partners and service providers, are vulnerable to damage from computer viruses, unauthorized access, hardware and software failures, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur, it could result in a material disruption of our product candidate development programs or manufacturing operations. For example, the loss of preclinical study or clinical trial data from completed, ongoing or planned trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. A significant interruption to our manufacturing operations could delay the completion of clinical trials and increase the costs of those trials. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

In the ordinary course of our business, we, our business partners and our service providers collect, process and store sensitive data, including intellectual property, clinical trial data, proprietary business information, personal data and personally identifiable information of our clinical trial subjects and employees. The secure processing, maintenance and transmission of this information is critical to our operations. Increased cybersecurity threats pose a risk to this information, in addition to our and our business partners' and service providers' systems and networks. Attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups, governments and individuals with a wide range of motives and expertise. We may also face increased cybersecurity risks due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we may be unable to anticipate these techniques or implement adequate preventative measures. We may also experience security breaches that may remain undetected for an extended period. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence.

Despite our security measures, our information technology and infrastructure may be vulnerable to cyber-attacks by hackers or internal bad actors, or breached due to employee error, a technical vulnerability, malfeasance or other disruptions that could have a negative impact, including loss or destruction of data (including confidential or critical business information). Although, to our knowledge, we have not experienced any such material security breach to date, we may experience cybersecurity incidents such as malware infections, ransomware, phishing attempts, thefts of personal, confidential, proprietary or other critical business information and other attempts at compromising our information technology that are typical for a company of our size in our market. Any security breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, significant regulatory penalties, and such an event could disrupt our operations, damage our reputation, result in significant expenses in implementing future security measures and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and financial results, and delay clinical development of our product candidates.

The UK's withdrawal from the EU has resulted in changes to regulatory requirements and has had and may continue to have a negative effect on global economic conditions, financial markets and our business, which could reduce the price of our shares.

Following a national referendum and enactment of legislation by the government of the UK, the UK formally withdrew from the EU on January 31, 2020, commonly referred to as "Brexit". Since the end of the Brexit transition period on January 1, 2021, Great Britain (England, Scotland and Wales) has not been directly subject to EU laws, however under the terms of the Protocol on Ireland and Northern Ireland, EU laws have generally applied to Northern Ireland. On February 27, 2023, the UK Government and the European Commission reached a political agreement on the "Windsor Agreement" which may revise the Protocol on Ireland and Northern Ireland in order to address some of the perceived shortcomings in its operation. Under the proposed changes, Northern Ireland would be reintegrated under the regulatory authority of the MHRA with respect to medicinal products. These proposed changes need to be codified and agreed by the respective parliaments of the UK and EU before taking effect. There could be additional uncertainty and risk around what these changes will mean to our business.

More generally, it is currently unclear to what extent the UK Government will seek to align its regulations with the EU. The EU laws that have been transposed into UK law through secondary legislation remain applicable in Great Britain. However, under the Retained EU Law (Revocation and Reform) Bill 2022, which is currently before the UK parliament, any retained EU law not expressly preserved and "assimilated" into domestic law or extended by ministerial regulations (to no later than June 23, 2026) will automatically expire and be revoked by December 31, 2023. In addition, new legislation such as the CTR is not applicable in Great Britain. Whilst the EU-UK Trade and Cooperation Agreement, or TCA, includes the mutual recognition of Good Manufacturing Practice, or GMP inspections of manufacturing facilities for medicinal products and GMP documents issued, it does not contain wholesale mutual recognition of UK and EU pharmaceutical regulations and product standards. There may be divergent local requirements in Great Britain from the EU in the future, which may impact clinical and development activities that occur in the UK in the future. Similarly, clinical trial submissions in the UK will not be able to be bundled with those of EU member states within the EMA Clinical Trial Information System, or CTIS, adding further complexity, cost and potential risk to future clinical and development activity in the UK. Significant political and economic uncertainty remains about how much the relationship between the UK and EU will differ as a result of the UK's withdrawal.

These developments, or the perception that any related developments could occur, have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets, and may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Any of these factors could depress economic activity and restrict our access to capital, which could have a material adverse effect on our business, financial condition and results of operations and reduce the price of our ordinary shares.

Companies established in Great Britain cannot use the centralized procedure and instead must follow one of the UK national authorization procedures or one of the remaining post-Brexit international cooperation procedures (such as the Access Consortium) to obtain an MA to market products in Great Britain. The MHRA may rely on a decision taken by the European Commission on the approval of a new (centralized procedure) MA when determining an application for a Great Britain MA; or use the MHRA's decentralized or mutual recognition procedures which enable MAs approved in EU member states (or Iceland, Liechtenstein, Norway) to be granted in Great Britain. Additionally, the 'Unfettered Access Procedure' enables an MA holder in Northern Ireland to seek recognition in Great Britain.

The full impact of these new arrangements and requirements, both on our existing processes and our ability to adjust our business and operations to operate successfully in the UK and EU, as well as more broadly on UK-EU cross-border trade and the economy, are expected to become clearer in the coming years. In particular, it remains to be seen whether the initial implementation of, and adjustment of UK-EU trading processes for, the TCA could disrupt or otherwise negatively impact our business and operations. These negative impacts could include amongst others a decrease in foreign direct investment in the UK, an increase of our costs, disruption of our supply chains, restrictions on

our ability to access capital and depression on economic activity or economic instability, which could in turn lead to a reduction in asset valuations, currency exchange rates and credit ratings.

In addition, the TCA has imposed additional restrictions on the free movement of people between the UK and the EU, which could have a material adverse effect on us, since we compete in these jurisdictions for well qualified employees in all aspects of our business. Any impact on our ability to attract new employees and to retain existing employees in their current jurisdictions could decrease our competitiveness. Any of these factors could have an adverse effect on our business, financial condition, results of operations, and prospects.

Risks Related to Our Ordinary Shares

The market price of our ordinary shares may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our ordinary shares.

Our share price is likely to be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your ordinary shares at or above your purchase price. The market price for our ordinary shares may be influenced by many factors, including:

- the success of competitive products or technologies;
- actual or expected changes in our growth rate relative to our competitors;
- results of clinical trials of our product candidates or those of our competitors;
- developments related to our existing or any future collaborations;
- regulatory or legal developments in the United States and other countries;
- development of new product candidates that may address our markets and make our product candidates less attractive;
- changes in physician, hospital or healthcare provider practices that may make our product candidates less useful;
- announcements by us, our partners or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- failure to meet or exceed financial estimates and projections of the investment community or that we provide to the public;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;

- actual or expected changes in estimates as to financial results, development timelines, recommendations by securities analysts or shifting investor perceptions;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions;
- changes in accounting principles; and
- the other factors described in this "Item 1A. Risk Factors" section and elsewhere in this Form 10-K.

In addition, the stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, when the market price of a security has been volatile, holders of that security have sometimes instituted securities class action litigation against the issuer. This risk is especially relevant for us because biopharmaceutical companies have experienced significant stock price volatility in recent years and during the COVID-19 pandemic. If any of the holders of our ordinary shares were to bring such a lawsuit against us, we could incur substantial costs defending the lawsuit and the attention of our senior management would be diverted from the operation of our business. Any adverse determination in litigation could also subject us to significant liabilities. Broad market and industry factors may negatively affect the market price of our ordinary shares, as well as general economic, political and market conditions such as recessions, interest rate changes or international currency fluctuations, regardless of our actual operating performance. Further, a decline in the financial markets and related factors beyond our control may cause the price of our ordinary shares to decline rapidly and unexpectedly. If the market price of our ordinary shares does not exceed your purchase price, you may not realize any return on your investment in us and may lose some or all of your investment.

Our executive officers, directors and principal shareholders, if they choose to act together, have the ability to significantly influence all matters submitted to shareholders for approval.

As of December 31, 2022, our executive officers, directors and shareholders who owned more than 5% of our outstanding ordinary shares and their respective affiliates, in the aggregate, hold ordinary shares representing approximately 40.0% of our outstanding ordinary shares. In addition, in connection with entering into the Financing Agreement, we issued to an affiliate of Perceptive Advisors, LLC, our largest shareholder that employs a director serving on our board, warrants to purchase an aggregate of 700,000 of our ordinary shares.

As a result, if these shareholders choose to act together, they would be able to significantly influence all matters submitted to our shareholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would significantly influence the election of directors, the composition of our management and approval of any merger, consolidation, sale of all or substantially all of our assets or other business combination that other shareholders may desire. Any of these actions could adversely affect the market price of our ordinary shares.

We are an "emerging growth company" and a "smaller reporting company," and the reduced disclosure requirements applicable to emerging growth companies and smaller reporting companies may make our ordinary shares less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 ("JOBS Act"), and may remain an emerging growth company until the last day of the fiscal year December 31, 2023, which represents the fifth year anniversary of our IPO. However, if certain events occur prior to the end of such five-year period,

including if we become a "large accelerated filer," our annual gross revenues exceed $1.07 billion or we issue more than $1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such five-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- reduced disclosure obligations relating to the presentation of financial statements in the "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure in our periodic reports filed with the SEC;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have elected to take advantage of this extended transition period.

We are also a smaller reporting company, and we will remain a smaller reporting company until the fiscal year following the determination that our voting and non-voting ordinary shares held by non-affiliates is more than $250 million measured on the last business day of our second fiscal quarter, or our annual revenues are more than $100 million during the most recently completed fiscal year and our voting and non-voting ordinary shares held by non-affiliates is more than $700 million measured on the last business day of our second fiscal quarter. Similar to emerging growth companies, smaller reporting companies are able to provide simplified executive compensation disclosure, are exempt from the auditor attestation requirements of Section 404, and have certain other reduced disclosure obligations, including, among other things, not being required to provide selected financial data, supplemental financial information or risk factors.

We may choose to take advantage of some, but not all, of the available exemptions for emerging growth companies and smaller reporting companies. We cannot predict whether investors will find our ordinary shares less attractive if we rely on these exemptions. If some investors find our ordinary shares less attractive as a result, there may be a less active trading market for our ordinary shares and our share price may be more volatile.

Anti-takeover provisions in our organizational documents and Cayman Islands law may discourage or prevent a change of control, even if an acquisition would be beneficial to our shareholders, which could depress the price of our ordinary shares and prevent attempts by our shareholders to replace or remove our current management.

Our memorandum and articles of association contain provisions that may discourage unsolicited takeover proposals that shareholders may consider to be in their best interests. Our board of directors is divided into three classes with staggered, three-year terms. Our board of directors has the ability to designate the terms of and issue preferred shares without shareholder approval. We are also subject to certain provisions under Cayman Islands law that could delay or prevent a change of control. Together these provisions may make more difficult the removal of management and may

discourage transactions that otherwise could involve payment of a premium over prevailing market prices for our ordinary shares.

There may be difficulties in enforcing foreign judgments against our management or us.

Certain of our directors and management reside outside the United States. A significant portion of our assets and such persons' assets are located outside the United States. As a result, it may be difficult or impossible for investors to effect service of process upon us within the United States or other jurisdictions, including judgments predicated upon the civil liability provisions of the federal securities laws of the United States.

In particular, investors should be aware that there is uncertainty as to whether the courts of the Cayman Islands or any other applicable jurisdictions would recognize and enforce judgments of U.S. courts obtained against us or our directors or management predicated upon the civil liability provisions of the securities laws of the United States or any state in the United States or entertain original actions brought in the Cayman Islands or any other applicable jurisdiction's courts against us or our directors or officers predicated upon the securities laws of the United States or any state in the United States.

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

Our corporate affairs and the rights of holders of ordinary shares are governed by Cayman Islands law, including the provisions of the Cayman Islands Companies Act (as amended), or the Companies Act, the common law of the Cayman Islands and by our memorandum and articles of association. We are also subject to the federal securities laws of the United States. The rights of shareholders to take action against the directors, actions by minority shareholders and the fiduciary responsibilities of our directors to us under Cayman Islands law are to a large extent governed by the common law of the Cayman Islands. The common law of the Cayman Islands is derived in part from comparatively limited judicial precedent in the Cayman Islands as well as from English common law, the decisions of whose courts are of persuasive authority, but are not binding on a court in the Cayman Islands. The rights of our shareholders and the fiduciary responsibilities of our directors under Cayman Islands law are different from what they would be under statutes or judicial precedent in some jurisdictions in the United States. In particular, the Cayman Islands has a different body of securities laws as compared to the United States, and certain states, such as Delaware, may have more fully developed and judicially interpreted bodies of corporate law. In addition, Cayman Islands companies may not have standing to initiate a shareholders derivative action in a Federal court of the United States.

As a result of all of the above, public shareholders may have more difficulty in protecting their interests in the face of actions taken by management, members of the board of directors or controlling shareholders than they would as public shareholders of a United States company.

We expect to be treated as resident in the UK for tax purposes, but may be treated as a dual resident company for UK tax purposes.

Our board of directors conducts our affairs so that the central management and control of the company is exercised in the UK. As a result, we expect to be treated as resident in the UK for UK tax purposes. Accordingly, we expect to be subject to UK taxation on our income and gains, except where an exemption applies.

However, we may be treated as a dual resident company for UK tax purposes. As a result, our right to claim certain reliefs from UK tax may be restricted, and changes in law or practice in the UK could result in the imposition of further restrictions on our right to claim UK tax reliefs.

We may be classified as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes, which could result in adverse U.S. federal income tax consequences to U.S. investors in our ordinary shares.

Based on the current and anticipated value of our assets, including goodwill, and the current and anticipated composition of our income, assets and operations, we do not believe we were a PFIC for the taxable year ended on December 31, 2022, and do not expect to be a PFIC for the current taxable year. However, the application of the PFIC rules is subject to uncertainty in several respects, and we cannot assure you that the U.S. Internal Revenue Service, or the IRS, will not take a contrary position. Furthermore, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. Accordingly, we cannot assure you that we were not a PFIC for our taxable year ended on December 31, 2022 or that we will not be a PFIC for our current taxable year or any future taxable year. A non-U.S. company will be considered a PFIC for any taxable year if (i) at least 75% of its gross income is passive income (including interest income), or (ii) at least 50% of the value of its assets (based on an average of the quarterly values of the assets during a taxable year) is attributable to assets that produce or are held for the production of passive income. The value of our assets generally is determined by reference to the market price of our ordinary shares, which may fluctuate considerably. In addition, the composition of our income and assets is affected by how, and how quickly, we spend any cash we raise. If we were to be classified as a PFIC for any taxable year during which a U.S. holder holds our ordinary shares, certain materially adverse U.S. federal income tax consequences could apply to such U.S. holder.

If a United States person is treated as owning at least 10% of our ordinary shares, such holder may be subject to adverse U.S. federal income tax consequences.

If a U.S. holder of our ordinary shares is treated as owning (directly, indirectly or constructively) at least 10% of the value or voting power of our ordinary shares, such U.S. holder may be treated as a "United States shareholder" with respect to each "controlled foreign corporation" in our group (if any). If our group includes one or more U.S. subsidiaries, certain of our non-U.S. subsidiaries could be treated as controlled foreign corporations (regardless of whether we are treated as a controlled foreign corporation). A United States shareholder of a controlled foreign corporation may be required to report annually and include in its U.S. taxable income its pro rata share of "Subpart F income," "global intangible low-taxed income" and investments in U.S. property by controlled foreign corporations, regardless of whether we make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. Failure to comply with these reporting obligations may subject you to significant monetary penalties and may prevent the statute of limitations from starting with respect to your U.S. federal income tax return for the year for which reporting was due. We cannot provide any assurances that we will assist investors in determining whether any of our non-U.S. subsidiaries is treated as a controlled foreign corporation or whether such investor is treated as a United States shareholder with respect to any of such controlled foreign corporations. Further, we cannot provide any assurances that we will furnish to any United States shareholders information that may be necessary to comply with the aforementioned reporting and tax payment obligations. U.S. holders of our ordinary shares should consult their tax advisors regarding the potential application of these rules to their investment in our ordinary shares.

Changes in tax laws or challenges to our tax position could adversely affect our results of operations and financial condition.

We are subject to complex tax laws that are subject to change or differing interpretations, including on a retroactive basis. Any such changes in tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate could adversely affect our tax position, including our effective tax rate or tax payments.

We have significant U.S. federal and state net operating losses, or NOLs, and UK carryforward tax losses which we may not be able to realize or which may be restricted under applicable law. We also benefit from certain tax incentive regimes, such as research and development tax credits. Any adverse change to these regimes, the application thereof or challenges to the tax position we have adopted under these rules could adversely affect our results of operations and financial condition.

As of December 31, 2022, we had federal and state NOL carryforwards in the United States of $63.8 million and $64.4 million, respectively, and cumulative carryforward tax losses in the UK of $187.9 million, which we expect to be available to reduce future taxable income subject to any relevant restrictions (including those in the U.S. and UK that limit the percentage of taxable income that can be reduced by NOLs and carried forward losses). The U.S. federal and state NOLs incurred prior to January 1, 2018 in the amount of approximately $1.0 million and $0.8 million, respectively, will begin to expire in 2036. U.S. federal NOLs generated after December 31, 2017 are not subject to expiration but such NOLs may only offset 80% of taxable income for taxable years beginning after December 31, 2020. As of December 31, 2022, we also had orphan drug and research and development credits in the U.S. in the amount of $9.4 million and research and development credits in the UK of $2.4 million. The UK carryforward tax losses will continue indefinitely, subject to relevant restrictions, under current UK legislation.

The NOLs and carryforward tax losses are subject to review and possible adjustment by the applicable tax authorities. Additionally, NOLs and UK carryforward tax losses, and research and development tax credits, may become subject to limitations in the event of certain cumulative changes in the ownership interest of significant shareholders, as determined under Sections 382 of the United States Internal Revenue Code, as well as the Corporation Tax Act 2010 Part 14 under the UK tax rules. This could limit the amount of NOLs or carryforward tax losses that we can utilize annually to offset future taxable income or tax liabilities. We have conducted a review of changes in the ownership interest of significant shareholders and determined that as of December 31, 2021, there were no limitations in the UK. However, for U.S. federal tax purposes, we have determined that ownership changes occurred in August 2016 and June 2018. We are still in the process of determining the annual limitation on NOLs as a result of such ownership changes. Subsequent ownership changes and changes to the U.S. federal or state or UK tax rules in respect of the utilization of NOLs and carryforward tax losses may further affect the limitation in future years.

General Risk Factors

We may engage in acquisitions that could disrupt our business, cause dilution to our shareholders or reduce our financial resources.

We have, and may in the future, enter into transactions to acquire other businesses, products or technologies. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our ordinary shares or other equity securities to the shareholders of the acquired company, which would reduce the percentage ownership of our existing shareholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and nondisruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

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

Owing to the international scope of our operations, fluctuations in exchange rates may adversely affect us, particularly between the U.S. dollar on the one hand, and the pound sterling and euro on the other hand. As a result, our business and the market price of our securities may be affected by such fluctuations, 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.

Our management team has broad discretion as to the use of the net proceeds from public and private equity or debt financings and the investment of these proceeds may not yield a favorable return. We may invest the proceeds in ways with which our shareholders disagree.

We have broad discretion in the application of any net proceeds we have received in the past or may receive in the future pursuant to existing or future equity and debt financings. Shareholders may not agree with our decisions, and our use of the proceeds and our existing cash and cash equivalents may not improve our results of operation or enhance the value of our ordinary shares. Our ability to apply certain proceeds may be restricted. For example, the proceeds provided under our Note Purchase Agreement may be used for working capital and general corporate purposes. Our failure to apply any such funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the market price of our ordinary shares to decline. In addition, until the net proceeds are used, they may be placed in investments that do not produce significant income or that may lose value. Additionally, our existing cash and cash equivalents are subject to general credit, liquidity, market and interest rate risks, which have been and may, in the future, be exacerbated by a U.S. and/or global financial crises. We may realize losses in the fair value of certain of our investments or a complete loss of these investments if the credit markets tighten, which would have an adverse effect on our results of operations, liquidity and financial condition.

We incur substantial costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly if we no longer qualify as an emerging growth company and smaller reporting company in the future, we incur and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, The Nasdaq Global Select listing requirements and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404, we engage in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants, adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing whether such controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we, or our independent registered public accounting firm if we no longer qualify as an emerging growth company, will not be able to conclude that our internal control over financial reporting is effective as required by Section 404. In addition, any testing by us conducted in connection with Section 404, or any 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. If we identify one or more material weaknesses or determine we have inadequate internal controls, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If securities or industry analysts cease to publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our ordinary shares, our share price and trading volume could decline.

The trading market for our ordinary shares relies in part on the research and reports that industry or securities analysts publish about us or our business. We do not control these analysts. Furthermore, if any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model, our intellectual property or our share performance, or if any of our preclinical studies or clinical trials and operating results fail to meet the expectations of analysts, our share price would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our share price or trading volume to decline.

Expectations relating to environmental, social and governance factors may impose additional costs and expose us to new risks.

There is an increasing focus from the SEC, stock exchanges, certain investors and other stakeholders concerning corporate responsibility, specifically related to environmental, social and governance factors. The SEC is considering and in some cases has proposed rules regarding new disclosure requirements relating to environmental, social and governance factors, and the SEC approved in 2021 new Nasdaq listing and disclosure requirements relating to board diversity that are applicable to us. Some investors may use these factors to guide their investment strategies and, in some cases, may choose not to invest in us if they believe our policies and disclosures relating to corporate responsibility are inadequate. Third-party providers of corporate responsibility ratings and reports on companies have varied and in some cases inconsistent standards. In addition, the criteria by which companies' corporate responsibility practices are assessed are evolving, which could result in greater expectations of us and cause us to undertake costly initiatives to satisfy such new criteria. Alternatively, if we elect not to or are unable to satisfy such new criteria or do not meet the criteria of a specific third-party provider, some investors may conclude that our policies with respect to corporate responsibility are insufficient. We may face reputational damage in the event that our corporate responsibility procedures or standards do not meet the standards set by various constituencies. Furthermore, if our competitors' corporate responsibility performance is perceived to be greater than ours, potential or current investors may elect to invest with our competitors instead. In addition, in the event that we communicate or disclose certain initiatives and goals regarding environmental, social and governance matters, we could fail, or be perceived to fail, in our achievement of such initiatives or goals, or we could be criticized for the scope of such initiatives or goals or be subject to litigation for such failures. If we fail to satisfy the expectations of investors and other stakeholders or our initiatives are not executed as planned, our reputation and financial results could be adversely affected.

Because we do not anticipate paying any cash dividends on our ordinary shares in the foreseeable future, capital appreciation, if any, would be your sole source of gain.

Under Cayman Islands law, we may only make distributions by way of dividend out of profits, or out of our share premium account (provided that immediately following the date that the dividend is proposed to be paid we are able to pay our debts as they fall due in the ordinary course of business). We have never declared or paid any cash dividends on our ordinary shares. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. In addition, the Note Purchase Agreement prohibits us from paying dividends during its term and the terms of existing and future financing agreements may also preclude us from paying dividends. As a result, capital appreciation, if any, of our ordinary shares would be your sole source of gain on an investment in our ordinary shares for the foreseeable future. See the "Dividend Policy" section of this Form 10-K for the year ended December 31, 2022 for additional information.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

Our principal office is located at 450 E[as]t 29th Street, New York, New York, USA, where we lease 22,721 square feet of office and laboratory space. We lease this office space under a lease that terminates on October 31, 2026.

We also own a long leasehold interest in the ground rights where our 29,000 square foot manufacturing facility is located, at 92 Britannia Walk, London, United Kingdom. The long leasehold interest expires in 2126, and there is no facility rent due.

Additionally, we lease an 11,306 square foot office facility located at 34-38 Provost Street, London, United Kingdom and 6,679 square feet of laboratory facilities at 15 Ebenezer Street, London, United Kingdom. The office space lease terminates on September 8, 2029 and the laboratory leases terminate on May 24, 2027. We also lease 10,126 square feet of office, laboratory and storage facilities at Paalbergweg 2-4, Amsterdam, Netherlands. The lease terminates on March 30, 2031.

In January 2021, we completed the acquisition of the buildings for our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility located in Buildings 2 and 3, Block K, Airport Avenue, Shannon Free Zone, Shannon, Ireland. The campus encompasses an aggregate of 150,000 square feet. We also entered into a lease for each property providing for a long leasehold interest that expires in 2211.

ITEM 3. LEGAL PROCEEDINGS

We are not subject to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our ordinary shares trade on the Nasdaq Global Select Market under the symbol "MGTX."

Holders of Record

As of March 8, 2023, there were 55 holders of record. The actual number of shareholders of our ordinary shares is greater than this number of record holders and includes shareholders who are beneficial owners but whose ordinary shares are held in street name by brokers and other nominees. This number of holders of record also does not include shareholders whose ordinary shares may be held in trust by other entities.

Dividend Policy

We have never declared or paid any cash dividends on our ordinary shares. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. In addition, the Note Purchase Agreement prohibits us from paying dividends during its term and the terms of existing and future financing agreements may also preclude us from paying dividends. However, if we do pay a cash dividend on our ordinary shares in the future, we will only pay such dividend out of our profits or share premium (subject to solvency requirements) as permitted under Cayman Islands law.

Recent Sales of Unregistered Securities

On November 9, 2022, we entered into a securities purchase agreement with Johnson and Johnson Innovation – JJDC, Inc., the investment arm of Johnson and Johnson ("JJDC"), pursuant to which we, in a private placement, agreed to issue and sell to JJDC an aggregate of 3,742,514 ordinary shares at a purchase price of $6.68 per share for gross proceeds of approximately $25.0 million.

The ordinary shares were issued in reliance on the exemption from registration provided by Section 4(a)(2) of the Securities Act of 1933, as amended.

ITEM 6. RESERVED

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of financial condition and operating results together with our financial statements and the related notes appearing in this Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many important factors, including those set forth in the section of this Form 10-K captioned "Item 1A. Risk Factors" and elsewhere in this Form 10-K, our actual results could differ materially from the results described in, or implied by, the forward-looking statements contained in the following discussion and analysis. For convenience of presentation some of the numbers have been rounded in the text below.

Overview

We are a vertically integrated, clinical stage gene therapy company with six programs in clinical development and a broad pipeline of preclinical and research programs. We have core capabilities in viral vector design and optimization and gene therapy manufacturing, as well as a potentially transformative gene regulation platform technology that allows precise, dose responsive control of gene expression by oral small molecules with dynamic range that can exceed 5000-fold. Led by an experienced management team, we have taken a portfolio approach by licensing, acquiring and developing technologies that give us depth across both product candidates and indications. Our initial focus is on three distinct areas of unmet medical need: ocular diseases, including both inherited retinal diseases as well as large degenerative ocular diseases, neurodegenerative diseases, and severe forms of xerostomia. Though initially focusing on the eye, central nervous system and salivary gland, we intend to expand our focus in the future to develop additional gene therapy treatments for patients suffering from a range of serious diseases.

We are an exempted company incorporated under the laws of the Cayman Islands in 2018, and prior to that, we commenced operations as MeiraGTx Limited, a private limited company incorporated under the laws of England and Wales in 2015. Our discussion of our financial condition and results of operations is based upon our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States ("GAAP"). Since our formation, we have devoted substantially all of our resources to developing our technology platform, establishing our viral vector manufacturing facilities and our cGMP plasmid and DNA production facility and developing manufacturing processes, advancing the product candidates in our ophthalmology, salivary gland and neurodegenerative disease programs, building our intellectual property portfolio, organizing and staffing our company, developing our business plan, raising capital, and providing general and administrative support for these operations. To date, we have financed our operations primarily with cash on hand and proceeds from the sales of our Series A ordinary shares, Convertible Preferred C Shares and ordinary shares. Through December 31, 2022, we received gross proceeds of approximately $471.0 million from sales of our ordinary shares, Series A ordinary shares and convertible preferred C shares, gross proceeds of approximately $75.0 million from issuance of debt and $130.0 million from the collaboration, option and license agreement with Janssen Pharmaceuticals, Inc. ("Janssen"), one of the Janssen Pharmaceuticals Companies of Johnson & Johnson (the "Collaboration Agreement"). As of December 31, 2022, we had cash and cash equivalents of $115.5 million, as well as $21.3 million we expect to receive from Janssen in the first quarter of 2023 in connection with the Collaboration Agreement.

We are a clinical stage company and have not generated any product revenues to date. We have six clinical programs and a pipeline of preclinical programs. Since inception, we have incurred significant operating losses. Our net losses for the years ended December 31, 2022 and 2021 were $129.6 million and $79.6 million, respectively. As of December 31, 2022, we had an accumulated deficit of $470.2 million. We do not expect to generate revenue from sales of products for several years, if at all. Under the Collaboration Agreement, we received an upfront payment in the amount of $100.0 million in March 2019 and a milestone payment in the amount of $30.0 million in December 2021. Additionally, pursuant to the Collaboration Agreement, we are eligible to receive research and development funding and additional potential milestone payments and royalties.

Our total operating expenses were $132.3 million and $110.5 million for the years ended December 31, 2022 and 2021, respectively. While we expect our operating expenses to continue to increase in connection with our ongoing development activities related to our product candidates, including the ongoing Phase 3 Lumeos clinical trial of botaretigene sparoparvovec for the treatment of patients with XLRP, we believe that certain of these increases will be partially offset by the research funding in connection with the Collaboration Agreement. In addition, we expect to continue incurring increasing costs associated with our clinical activities for AAV-hAQP1 for the treatment of radiation-induced xerostomia and xerostomia associated with Sjogren's syndrome, as well as for AAV-GAD for the treatment of Parkinson's disease. We also incurred expenses during the year ended December 31, 2022 and expect to continue to incur expenses related to research activities in additional therapeutic areas to expand our pipeline, developing our potentially transformative gene regulation technology, hiring additional personnel as needed in manufacturing, research, clinical operations, quality and other functional areas, and associated cash and share-based compensation expense, as

well as the further development of internal manufacturing capabilities and capacity and other associated costs including the management of our intellectual property portfolio.

On August 2, 2022 we, as borrower, and the Subsidiary Guarantors, entered into the Financing Agreement by and among the Company, the Subsidiary Guarantors, the lenders and other parties from time to time party thereto and Perceptive, as administrative agent and lender. On December 19, 2022, the Financing Agreement was converted to a Note Purchase Agreement between the same parties and under substantially the same terms and conditions as the Financing Agreement, subject to certain customary note constitution terms.

The Note Purchase Agreement provides for the issuance of the Tranche 1 Notes in an initial amount of $75.0 million, and we may request the issuance of the Tranche 2 Notes in an additional amount of $25.0 million to be made available at Perceptive's sole discretion before August 2, 2024. The Note Purchase Agreement matures on August 2, 2026 and is interest-only during the term. We have the option to redeem outstanding principal notes at any time along with an applicable early redemption fee. Outstanding amounts under the Note Purchase Agreement bear interest at a fluctuating rate per annum equal to 10.00% plus the secured overnight financing rate administered by the Federal Reserve Bank of New York for a one-month tenor, subject to a 1.00% floor.

On November 9, 2022, we entered into a securities purchase agreement with JJDC, pursuant to which we, in a private placement, agreed to issue and sell to JJDC an aggregate of 3,742,514 ordinary shares at a purchase price of $6.68 per share for gross proceeds of approximately $25.0 million.

We will require additional capital in the future, which we may raise through equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources to enable us to complete the development and potential commercialization of our product candidates. Furthermore, we expect to continue incurring costs associated with being a public company. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative effect on our financial condition and our ability to pursue our business strategy. In addition, attempting to secure additional financing may divert the time and attention of our management from day-to-day activities and harm our product candidate development efforts. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate certain of our research and development programs.

Based on our cash and cash equivalents at December 31, 2022 and the research funding and milestone payments we expect to receive under the Collaboration Agreement, we estimate that such funds will be sufficient to enable us to fund our operating expenses and capital expenditure requirements through the fourth quarter of 2024. We have based these estimates on assumptions that may prove to be wrong, and we may use our available capital resources sooner than we currently expect. See "Liquidity and Capital Resources." Because of the numerous risks and uncertainties associated with the development of our product candidates, any future product candidates, our platform and technology and because the extent to which we may enter into collaborations with third parties for development of any of our product candidates is unknown, we are unable to estimate the amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates.

Adequate additional funds may not be available to us on acceptable terms, or at all. To the extent that we raise additional capital through the sale of equity or convertible securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. Any future debt financing or preferred equity or other financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could potentially dilute your ownership interests.

If we raise additional funds through collaborations, strategic alliances, or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or

product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce, or terminate our product development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Because of the numerous risks and uncertainties associated with drug development, we are unable to 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 revenue from 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.

Highlights and Recent Developments

Recent Development Highlights and Anticipated 2023 Milestones

Botaretigene Sparoparvovec for the Treatment of XLRP:

- On October 1, 2022, clinical data from a Phase 1/2 MGT009 clinical trial (NCT03252847) were presented in a late-breaking oral presentation at the Retina Subspecialty Day program of the AAO 2022 Annual Meeting; treatment with botaretigene sparoparvovec was found to have an acceptable safety profile and efficacy assessments in this study and demonstrated improvements in retinal sensitivity, visual function and functional vision.[1]
- Further sensitivity analysis was conducted on study participants by applying the Phase 3 Lumeos (NCT04671433) study eligibility criteria that corroborated the endpoints selected for the Phase 3 study.[1]
- We, in collaboration with Janssen, are dosing patients in the pivotal Phase 3 Lumeos clinical trial of botaretigene sparoparvovec and remain on track for a BLA submission in 2024.

[1] Michaelides, M et al. Ph1/2 AAV5-RPGR (Botaretigene Sparoparvovec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP). Abstract #30071754. Presented at the 2022 American Academy of Ophthalmology Annual Meeting.

AAV-hAQP1 for the Treatment of Grade 2/3 Radiation-Induced Xerostomia:

- We reported positive clinical data from the AQUAx Phase 1 clinical trial in December 2022.
    - Clinically meaningful improvements in xerostomia symptoms and disease burden in two validated Patient-Reported Outcome (PRO) measures in both unilateral and bilateral treated cohorts were demonstrated.
        - 18/24, or 75% achieved clinically meaningful symptom improvement using the Global Rate of Change (GRCQ) PRO.
        - Using the Xerostomia Questionnaire (XQ), 71% (17/24) reported an improvement of >8 points (clinically meaningful), and 67% (16/24) had an improvement of ≥10 (considered transformative by KOLs).
    - Meaningful increases in whole saliva flow rates were observed post-treatment, providing objective evidence of the biological activity of AAV-hAQP1 treatment.
    - Early long-term follow-up data suggest durability of improvement 2+ years post-treatment.
    - AAV-hAQP1 appears safe and well-tolerated at each dose tested.
- All participants are followed for 1 year post-treatment and then enter a long-term follow-up study for another 4 years.
- We intend to present the final 12 month data from the bilateral treated cohorts from the AQUAx Phase 1 study in the second quarter of 2023.
- Based on the favorable safety and efficacy profile of AAV-hAQP1 in the AQUAx Phase 1 study, we intend to initiate a randomized, double-blind, placebo-controlled, Phase 2 study evaluating the bilateral administration of two active doses of AAV-hAQP1 in the second quarter of 2023.

AAV-GAD for the Treatment of Parkinson's Disease:

- We are now dosing patients in the AAV-GAD clinical trial under a new IND using material manufactured in our cGMP facility in London, United Kingdom using our proprietary production process.
- The AAV-GAD trial is a three-arm randomized Phase 1 clinical bridging study with subjects randomized to one of two doses of AAV-GAD or sham control.
- The objective of the AAV-GAD trial (NCT05603312) is to evaluate the safety and tolerability of AAV-mediated delivery of glutamic acid decarboxylase (GAD) gene transfer into the subthalamic nuclei (STN) of participants with Parkinson's disease.
- Completion of enrollment is anticipated by the third quarter of 2023.

Riboswitch Gene Regulation Platform & Vector Engineering:

- We exhibited 15 poster presentations at the European Society of Gene and Cell Therapy 2022 Annual Congress, which included data from our novel gene regulation platform, including the first data demonstrating the potential to regulate cell therapies including CAR-T, as well as data from our promoter platforms and several new, optimized pre-clinical programs addressing severe unmet needs for indications such as amyotrophic lateral sclerosis (ALS) and Wilson's disease. In addition, we made several presentations on our proprietary viral vector manufacturing technology and potency assay development.
- Our next-generation riboswitch-based gene regulation platform can be used to precisely control the expression of any gene delivered in any context with an unprecedented dynamic range using novel, synthetic, orally delivered small molecules.
- We now have over 30 novel orally available small molecules with high specificity and potency to our riboswitch aptamers moving through PK, biodistribution and toxicology studies, with the first GMP material for IND currently being manufactured.

Gene Therapy Manufacturing:

- Our wholly-owned facilities have now produced GMP clinical trial material for 6 different indications, using multiple AAV serotypes, including administration into the eye, salivary gland and central nervous system.
- We believe that our proprietary platform production process has produced one of the highest yields and full ratios in the industry.
- We believe that bringing all aspects of testing and vector production in-house reduces regulatory risk, ensures the highest quality of products, lowers costs and helps avoid bottlenecks in clinical development.
- In addition to our 30,000-square-foot facility in London, we now have a 150,000-square-foot plant in Shannon, Ireland which contains three facilities: one built to be flexible and scalable for viral vector production, another to manufacture plasmid DNA – the critical starting material for producing gene therapy products – and third, a Quality Control (QC) hub performing advanced biochemical quality control testing appropriate for commercialization.

Components of Our Results of Operations

License Revenue

Our license revenue consisted of the amortization of the upfront and milestone payments we received in connection with the Collaboration Agreement.

Operating Expenses

Our operating expenses since inception have consisted primarily of general and administrative costs and research and development costs.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, legal, business development and administrative functions. General and administrative expenses also include legal fees relating to intellectual property and corporate matters; professional fees for accounting, auditing, tax and consulting services; insurance costs; travel expenses; and office facility-related expenses, which include direct depreciation costs.

We expect that our general and administrative expenses will increase in the future as we increase our personnel headcount to support increased research and development activities. We have also incurred and expect to continue to incur increased expenses associated with being a public company, including costs of accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with Nasdaq and SEC requirements; director and officer insurance costs; and investor and public relations costs.

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:

- employee-related expenses, including salaries, benefits and travel of our research and development personnel;
- expenses incurred in connection with third-party vendors that conduct clinical and preclinical studies and manufacture the drug product for the clinical trials and preclinical activities;
- acquisition of in process research and development;
- costs associated with clinical and preclinical activities including costs related to facilities, supplies, rent, insurance, certain legal fees, share-based compensation, and depreciation; and
- expenses incurred with the development and operation of our manufacturing facilities.

We expense research and development costs as incurred.

Research and development activities are central to our business model. We expect that our research and development expenses will continue to increase substantially for the foreseeable future as we initiate additional preclinical and clinical trials of our existing product candidates, including the ongoing Phase 3 Lumeos trial of botaretigene sparoparvovec for the treatment of patients with XLRP, and continue to discover and develop additional product candidates. Certain of these increases in research and development costs will be partially offset by the research funding provided in connection with the Collaboration Agreement we entered into in January 2019. In addition, we expect to continue incurring increasing research and development costs associated with our clinical activities for AAV-hAQP1 for the treatment of radiation-induced xerostomia and xerostomia associated with Sjogren's syndrome, as well as for AAV-GAD for the treatment of Parkinson's disease.

We cannot determine with certainty the duration and costs of future clinical trials of our product candidates or any other product candidate we may develop or if, when, or to what extent we will generate revenue from the commercialization and sale of any product candidate for which we obtain marketing approval. We may never succeed in obtaining marketing approval for any product candidate. The duration, costs and timing of clinical trials and development of our existing product candidates or any other product candidate we may develop will depend on a variety of factors, including:

- the scope, rate of progress, expense and results of clinical trials of our existing product candidates, as well as of any future clinical trials of other product candidates and other research and development activities that we may conduct;

- uncertainties in clinical trial design and patient enrollment rates;

- the actual probability of success for our product candidates, including the safety and efficacy, early clinical data, competition, manufacturing capability and commercial viability;

- significant and changing government regulation and regulatory guidance;

- the timing and receipt of any marketing approvals; and

- the expense of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or another U.S. or foreign regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in our clinical trials due to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development.

Other non-operating income (expense)

Other non-operating income (expense) includes the following:

Foreign currency (loss) gain

Our consolidated financial statements are presented in U.S. dollars, which is our reporting currency. The financial position and results of operations of our subsidiaries MeiraGTx UK II Limited, MeiraGTx Ireland DAC, MeiraGTx Netherlands B.V., MeiraGTx B.V. and MeiraGTx Belgium are measured using the foreign subsidiaries' local currency as the functional currency. These entities' cash accounts holding U.S. dollars and intercompany payables and receivables are remeasured based upon the exchange rate at the date of remeasurement with the resulting gain or loss included in the consolidated statement of operations and comprehensive loss.

Other comprehensive income

Other comprehensive income includes the following:

Foreign currency translation gain

Expenses of subsidiaries have been translated into U.S. dollars at average exchange rates prevailing during the period. Assets and liabilities have been translated at the rates of exchange on the consolidated balance sheet date. The resulting translation gain adjustments are recorded directly as a separate component of shareholders' equity and as other comprehensive loss on the consolidated statements of operations and comprehensive loss.

Critical Accounting Policies and Use of Estimates

Management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of these consolidated financial statements requires us to make estimates and judgements that affect the reporting amounts of assets, liabilities and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgements, including those related to license and collaboration revenue, share-based compensation and accrued expenses. We base our estimates on historical experience, known trends and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgements about the carrying value of assets and liabilities that are not readily apparent from our sources. Actual results may differ from these estimates under different assumptions.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing in this Form 10-K, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our financial statements.

Collaboration Arrangements

We evaluate our collaborative arrangements pursuant to Accounting Standards Codification ("ASC") 808, *Collaborative Arrangements* ("ASC 808") and ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). We consider the nature and contractual terms of collaborative arrangements and assess whether the arrangement involves a joint operating activity pursuant to which we are an active participant and are exposed to significant risks and rewards with respect to the arrangement. If we are an active participant and exposed to significant risks and rewards with respect to the arrangement, we account for the arrangement as a collaboration under ASC 808. To date, we have entered into two separate collaboration agreements, both of which are with Janssen, which were determined to be within the scope of ASC 808.

ASC 808 does not address recognition or measurement matters related to collaborative arrangements. Payments between participants pursuant to a collaborative arrangement that are within the scope of other authoritative accounting literature on income statement classification are accounted for using the relevant provisions of that literature. If the payments are not within the scope of other authoritative accounting literature, the income statement classification for the payments is based on an analogy to authoritative accounting literature or if there is no appropriate analogy, a reasonable, rational and consistently applied accounting policy election. Payments received from a collaboration partner to which this policy applies may include upfront payments in respect of a license of intellectual property, development and commercialization-based milestones, and royalties.

Revenue Recognition

Arrangements with collaborators may include licenses to intellectual property, research and development services, manufacturing services for clinical and commercial supply, and participation on joint steering committees. We evaluate the promised goods or services to determine which promises, or group of promises, represent performance obligations. In contemplation of whether a promised good or service meets the criteria required of a performance obligation, we consider the stage of development of the underlying intellectual property, the capabilities and expertise of the customer relative to the underlying intellectual property, and whether the promised goods or services are integral to or dependent on other promises in the contract. When accounting for an arrangement that contains multiple performance obligations, we must develop judgmental assumptions, which may include market conditions, reimbursement rates for personnel costs, development timelines and probabilities of regulatory success to determine the stand-alone selling price for each performance obligation identified in the contract.

When we conclude that a contract should be accounted for as a combined performance obligation and recognized over time, we must then determine the period over which revenue should be recognized and the method by which to measure revenue. We generally recognize revenue using a cost-based input method.

The Collaboration Agreement is accounted for under ASC 808, however, as ASC 808 does not address recognition or measurement matters such as determining the appropriate unit of accounting or when the recognition criteria are met, we account for the consideration received from Janssen in accordance with ASC 606. In accordance with ASC 606, we recognize revenue when the customer or collaborator obtains control of promised goods or services, in an amount that reflects the consideration which we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of ASC 606, 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;

iv. allocate the transaction price to the performance obligations within the contract; and

v. recognize revenue when (or as) the entity satisfies a performance obligation.

We only apply the five-step model to contracts when we determine that it is probable we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

At contract inception, once the contract is determined to be by analogy within the scope of ASC 606, we assess the goods or services promised within the contract to determine whether each promised good or service is a performance obligation. The promised goods or services for our arrangements typically consist of a license to our intellectual property and research, development and manufacturing services. We may provide options to additional items in such arrangements, which are accounted for as separate contracts when the customer elects to exercise such options, unless the option provides a material right to the customer. Performance obligations are promises in a contract to transfer a distinct good or service to the customer that (i) the customer can benefit from on its own or together with other readily available resources, and (ii) is separately identifiable from other promises in the contract. Goods or services that are not individually distinct performance obligations are combined with other promised goods or services until such combined group of promises meet the requirements of a performance obligation.

We determine transaction prices based on the amount of consideration we expect to receive for transferring the promised goods or services in the contract. Consideration may be fixed, variable, or a combination of both. At contract inception for arrangements that include variable consideration, we estimate the probability and extent of consideration we expect to receive under the contract utilizing either the most likely amount method or expected amount method, whichever best estimates the amount expected to be received. We then consider any constraints on the variable consideration and include in the transaction price variable consideration to the extent it is deemed probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

We then allocate the transaction price to each performance obligation based on the relative standalone selling price and recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) control is transferred to the customer and the performance obligation is satisfied. For performance obligations which consist of licenses and other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at

a point in time and, if over time, the appropriate method of measuring progress. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

We record amounts as accounts receivable when the right to consideration is deemed unconditional. When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded as deferred revenue.

Amounts received prior to satisfying the revenue recognition criteria are recognized as deferred revenue in our consolidated balance sheet. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue – related party, current. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue – related party.

Income Taxes

Since we have recurring losses and a valuation allowance against deferred tax assets, there was no tax expense (benefit) for the years ended December 31, 2022 and 2021.

Research and Development

Research and development costs are charged to expense as incurred. These costs include, but are not limited to, employee-related expenses, including salaries, benefits and travel of our research and development personnel; expenses incurred under agreements with contract research organizations and investigative sites that conduct clinical and preclinical studies and manufacture the drug product for the clinical studies and preclinical activities; acquisition of in-process research and development; facilities; supplies; rent, insurance, certain legal fees, stock-based compensation, depreciation and other costs associated with clinical and preclinical activities and regulatory operations. Research funding under collaboration agreements and refundable research and development credits / tax credits received are recorded as an offset to these costs.

Costs for certain development activities, such as outside research programs funded by us, are recognized based on an evaluation of the progress to completion of specific tasks with respect to their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development expense, as the case may be.

Share-Based Compensation

Options

We grant share options to employees, non-employee members of our board of directors and non-employee consultants as compensation for services performed. Employee and non-employee members of the board of directors' awards of share-based compensation are accounted for in accordance with ASC 718, *Compensation—Stock Compensation*, or ASC 718. ASC 718 requires all share-based payments to employees and non-employee directors, including grants of share options, to be recognized in the statement of operations and comprehensive loss based on their grant date fair values. The grant date fair value of share options is estimated using the Black-Scholes option valuation model.

Using this model, fair value is calculated based on assumptions with respect to (i) the fair value of our ordinary shares on the grant date; (ii) expected volatility of our ordinary share price, (iii) the periods of time over which employees and members of our board of directors are expected to hold their options prior to exercise (expected term), (iv) expected dividend yield on our ordinary shares, and (v) risk-free interest rates.

Our ordinary shares were not traded on a public exchange prior to our IPO in June 2018. Therefore, we believe that our future volatility will differ materially during the expected term from the volatility that would be calculated from our historical share prices to date. Consequently, expected volatility is based on an analysis of guideline companies in accordance with ASC 718. The expected dividend yield is zero as we have never paid dividends and do not currently anticipate paying any in the foreseeable future. Risk-free interest rates are based on quoted U.S. Treasury rates for securities with maturities approximating the option's expected term.

Restricted Share Units

The Company grants restricted share units ("RSUs") to employees, non-employee members of our board of directors and non-employee consultants as compensation for services performed. Awards of RSUs are accounted for in accordance with ASC 718, *Compensation - Stock Compensation,* or ASC 718. ASC 718 requires all share-based payments to employees and non-employee directors, including grants of RSUs, to be recognized in the consolidated statement of operations and comprehensive loss based on their grant date fair values. The grant date fair value of RSUs is determined using the closing market price of the Company's ordinary shares on the date of grant.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

	2022	2021	Change
		(in thousands)	
License revenue - related party	$ 15,920	$ 37,701	$ (21,781)
Operating expenses:			
General and administrative	46,550	43,765	2,785
Research and development	85,725	66,694	19,031
Total operating expenses	132,275	110,459	21,816
Loss from operations	(116,355)	(72,758)	(43,597)
Other non-operating income (expense)			
Foreign currency loss	(9,452)	(6,293)	(3,159)
Interest income	777	212	565
Interest expense	(4,946)	(288)	(4,658)
Fair value adjustments	361	(434)	795
Net loss	(129,615)	(79,561)	(50,054)
Other comprehensive income:			
Foreign currency translation gain	8,718	2,226	6,492
Comprehensive loss	$ (120,897)	$ (77,335)	$ (43,562)

License Revenue

License revenue was $15.9 million for the year ended December 31, 2022, compared to $37.7 million for the year ended December 31, 2021. This decrease is a result of the Company receiving a $30.0 million milestone payment in connection with the Collaboration Agreement during the year ended December 31, 2021.

General and Administrative Expenses

General and administrative expenses were $46.6 million for the year ended December 31, 2022, compared to $43.8 million for the year ended December 31, 2021. The increase of $2.8 million was primarily due to an increase of $3.4 million in share-based compensation, $2.0 million in legal and accounting fees, $1.3 million in consulting fees and $0.4 million in depreciation. These increases were partially offset by a decrease of $1.7 million in payroll and payroll-

related costs, $1.2 million in insurance, $0.8 million in rent and facilities costs and $0.6 million in other general and administrative costs.

Research and Development Expenses

Research and development expenses for the years ended December 31, 2022 and 2021 were as follows (in millions):

	2022	2021	Change
Gross research and development expenses	$ 165.8	$ 141.1	$ 24.7
Janssen reimbursements	(73.3)	(69.0)	(4.3)
Tax incentive reimbursement	(6.8)	(5.4)	(1.4)
Research and development expenses	$ 85.7	$ 66.7	$ 19.0

Gross research and development expenses for the year ended December 31, 2022 increased $24.7 million as compared to the prior year primarily due to an increase of $8.9 million in costs related to the manufacturing of our clinical trial materials, $6.5 million in payroll and payroll-related costs, $4.6 million in costs related to our pre-clinical research and clinical trials, $4.5 million in share-based compensation, $2.7 million in rent and facility costs, $0.5 million in depreciation and $1.1 million in other research costs. These increases were partially offset by a decrease of $2.6 million in license fees and $1.5 million in acquired research and development costs.

Reimbursements under the Collaboration Agreement for the year ended December 31, 2022 increased $4.3 million as compared to the prior year primarily due to an increase in activity in the programs licensed under the Collaboration Agreement.

Tax incentive reimbursement for the year ended December 31, 2022 increased $1.4 million as compared to the prior year primarily due to the increase in allowable research and development costs.

Foreign Currency Loss

Foreign currency loss was $9.5 million for the year ended December 31, 2022 compared to a loss of $6.3 million for the year ended December 31, 2021. The increase in the loss of $3.2 million was primarily due to an unrealized loss on the valuation of the Company's intercompany payables and receivables due to the strengthening of the U.S. dollar against the pound sterling and euro during the year ended December 31, 2022.

Interest Income

Interest income was $0.8 million for the year ended December 31, 2022 compared to $0.2 million for the year ended December 31, 2021. The increase was due to a higher interest rate during 2022.

Interest Expense

Interest expense was $4.9 million for the year ended December 31, 2022 compared to $0.3 million for the year ended December 31, 2021. The increase was primarily due to the interest on the Financing Agreement entered into in August 2022, which was later converted to a Note Purchase Agreement in December 2022.

Other Comprehensive Income – Foreign Currency Translation Gain

Foreign currency translation adjustments resulted in a translation gain of $8.7 million for the year ended December 31, 2022 compared to a translation gain of $2.2 million for the year ended December 31, 2021. The change in the amount of $6.5 million was primarily due to a strengthening of the U.S. dollar against the pound sterling and euro during the year ended December 31, 2022.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. For the year ended December 31, 2022, we used $73.1 million in cash flows from operations. We did not generate positive cash flows from operations during the year and there are no assurances that we will generate positive cash flows in the future. Additionally, there are no assurances that we will be successful in obtaining an adequate level of financing for the development and commercialization of our product candidates. We expect to incur significant expenses and operating losses for the foreseeable future as we advance the preclinical and clinical development of our product candidates. We expect that our research and development and general and administrative costs will increase in connection with conducting preclinical studies and clinical trials for our product candidates, building out internal capacity to have products manufactured to support preclinical studies and clinical trials, expanding our intellectual property portfolio, and providing general and administrative support for our operations. In addition, on August 4, 2020 we entered into agreements to acquire the buildings for our second, large scale cGMP viral vector manufacturing facility and our first cGMP plasmid and DNA production facility in Shannon, Ireland to expand our manufacturing and supply chain capabilities. We closed on the acquisition of the first building in August 2020 and closed on the second building in January 2021. As a result of these incurred and expected expenses we will need additional capital to fund our operations, which we may obtain from additional equity or debt financings, collaborations, licensing arrangements, or other sources.

We do not currently have any approved products and have never generated any revenue from product sales. We have historically financed our operations primarily through cash on hand and proceeds from the sale of our ordinary shares, series A ordinary shares and convertible preferred C shares. In March 2019 and December 2021, we received a $100.0 million upfront payment and a $30.0 million milestone payment, respectively, in connection with the Collaboration Agreement, which also provides us with research funding, and we are eligible to receive additional potential milestone payments and royalties.

Additionally, on August 2, 2022, we, as borrower, and our Subsidiary Guarantors, entered into a Financing Agreement by and among us, the Subsidiary Guarantors, the lenders and other parties from time to time party thereto and Perceptive, as administrative agent and lender. On December 19, 2022, the Financing Agreement was converted to a Note Purchase Agreement between the same parties and under substantially the same terms and conditions as the Financing Agreement, subject to certain customary note constitution terms.

The Note Purchase Agreement provides for the issuance of the Tranche 1 Notes in an initial amount of $75.0 million, and we may request the issuance of the Tranche 2 Notes in an additional amount of $25.0 million to be made available at Perceptive's sole discretion before August 2, 2024. The Note Purchase Agreement matures on August 2, 2026 and is interest-only during the term. We have the option to redeem outstanding principal notes at any time along with an applicable early redemption fee. Outstanding amounts under the Note Purchase Agreement bear interest at a fluctuating rate per annum equal to 10.00% plus the secured overnight financing rate administered by the Federal Reserve Bank of New York for a one-month tenor, subject to a 1.00% floor.

Our obligations under the Note Purchase Agreement are secured by our London, UK and Shannon, Ireland manufacturing facilities, $3.0 million of our cash and the bank accounts of the Subsidiary Guarantors, and the issued and outstanding equity interests of the Subsidiary Guarantors.

The Note Purchase Agreement imposes covenants that include, among other things, enrolling in a Phase III trial for AAV-RPGR on or before June 30, 2023, and ensuring the Company's Shannon manufacturing facility meets or satisfies all applicable good manufacturing practice requirements on or before December 31, 2023, as well as various restrictions on us and the Subsidiary Guarantors, including restrictions pertaining to: (i) the incurrence of additional indebtedness, (ii) limitations on liens, (iii) limitations on certain investments, (iv) making distributions, dividends and other payments, (v) mergers, consolidations and acquisitions, (vi) dispositions of assets, (vii) our maintenance of at least $3 million in a U.S. bank account, (viii) transactions with affiliates, (ix) changes to governing documents, (x) changes to certain agreements and leases and (xi) changes in control; however, certain of these restrictions contain exceptions which allow us to license, sell and monetize assets in our AAV-hAQP1 program in development to treat radiation-induced xerostomia, our AAV-GAD program in development to treat Parkinson's disease and our gene regulation platform technologies.

In connection with entering into the Financing Agreement, we granted warrants (the "Warrants") to Perceptive to purchase up to (i) 400,000 ordinary shares of the Company at an exercise price of $15.00 per share and (ii) 300,000 ordinary shares of the Company at an exercise price of $20.00 per share. The Warrants will expire on August 2, 2027.

Based on our current cash, cash equivalents and accounts receivable – related party at December 31, 2022 and the research funding and milestone payments we expect to receive under the Collaboration Agreement, we estimate that we will be able to fund our operating expenses and capital expenditure requirements through the fourth quarter of 2024. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect.

Cash Flows

We had $115.5 million and $137.7 million of cash and cash equivalents as of December 31, 2022 and 2021, respectively.

The following table summarizes our sources and uses of cash for the period presented:

	For the Years Ended December 31,	
	2022	2021
	(in thousands)	
Net cash used in operating activities	$ (73,098)	$ (10,530)
Net cash used in investing activities	(44,963)	(61,717)
Net cash provided by financing activities	95,200	1,708
Net decrease in cash and cash equivalents	$ (22,861)	$ (70,539)

Operating Activities

During the year ended December 31, 2022, our cash used in operating activities of $73.1 million was primarily due to our net loss of $129.6 million as we incurred expenses associated with research activities on our clinical programs, manufacturing of our clinical trial materials, preclinical research programs and general and administrative expenses. The net loss included non-cash charges of $46.9 million, which consisted of $28.6 million of share-based compensation, $9.5 million of a foreign currency loss, $8.7 million of depreciation and amortization, $0.4 million of a fair value downward adjustment, $0.2 million of negative net change in right-of-use assets and liabilities, $0.2 million of amortization of interest on asset retirement obligations and $0.4 million of amortization of the debt discount. Additionally, operating assets, consisting of accounts receivable-related party, prepaid expenses, tax incentive receivable, other current assets and other assets, decreased by $5.2 million and operating liabilities, consisting of accounts payable, accrued expenses, and deferred revenue-related party, decreased by $4.4 million.

During the year ended December 31, 2021, our cash used in operating activities of $10.5 million was primarily due to our net loss of $79.6 million as we incurred expenses associated with research activities on our clinical programs, manufacturing of our clinical trial materials, preclinical research programs and general and administrative expenses. The net loss included non-cash charges of $37.8 million, which consisted of $20.8 million of share-based compensation, $6.3 million of a foreign currency loss, $7.9 million of depreciation and amortization, $1.0 million of shares issued in connection with a license agreement, $1.0 million of shares issued in connection with an asset acquisition, $0.4 million of a fair value adjustment, $0.2 million of net change in right-of-use assets and liabilities, $0.1 million of amortization of interest on asset retirement obligations and $0.1 million of loss on disposal of equipment, furniture and fixtures. Additionally, operating assets, consisting of accounts receivable-related party, prepaid expenses, tax incentive receivable, other current assets and other assets, decreased by $17.3 million and operating liabilities, consisting of accounts payable, accrued expenses, and deferred revenue-related party, increased by $14.0 million.

Investing Activities

Net cash used in investing activities for the year ended December 31, 2022 of $45.0 million consisted of purchases of property and equipment for our manufacturing, laboratory and process development facilities and buildout costs of our new facilities in Ireland.

Net cash used in investing activities for the year ended December 31, 2021 of $61.7 million consisted primarily of $8.9 million in payments for the acquisition of the second building and long-term lease of our manufacturing facility in Ireland, $6.5 million in connection with equity method and other investments and $46.3 million for purchases of property and equipment for our manufacturing, laboratory and process development facilities and buildout costs of our new facilities in Ireland.

Financing Activities

Net cash provided by financing activities was $95.2 million for the year ended December 31, 2022, which consisted primarily of $75.0 million from issuance of the Tranche 1 Notes, $25.0 million from the issuance of ordinary shares and $0.2 million in exercise of share options, which was offset by $2.8 million of payments for withholdings of shares for income taxes, and financing fees of $2.2 million.

Net cash provided by financing activities was $1.7 million for the year ended December 31, 2021, which is primarily from the exercise of share options.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements under applicable SEC rules and do not have any holdings in variable interest entities.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012, (the "JOBS Act"), permits an "emerging growth company," which we are, to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected to take advantage of this extended transition period through December 31, 2023.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

We are exposed to market risks in the ordinary course of our business. These risks primarily include foreign currency exchange rate sensitivities and interest rate risk.

Foreign Currency Exchange Risk

We currently operate in the United States, the United Kingdom, the Netherlands, Ireland and Belgium. Our activities in these jurisdictions expose us to currency exchange rate fluctuations primarily between the U.S. Dollar and the British pound sterling and euro. When the U.S. Dollar strengthens against these currencies, the U.S. Dollar value of non-U.S. Dollar based losses increases. To the extent that our international activities recorded in local currencies increase in the future, our exposure to fluctuations in currency exchange rates will correspondingly increase. With respect to our foreign currency exposures as of December 31, 2022, we estimate a 10% unfavorable movement in foreign currency exchange rates would have the effect of creating an additional foreign currency loss of approximately $28.1 million within other non-operating income (expense) for the year ended December 31, 2022.

Interest Rate Risk

We are exposed to market risk as a result of changes in interest rates applicable to borrowings under our Note Purchase Agreement. Borrowings under the Note Purchase Agreement bear interest at a fluctuating rate per annum equal to 10.00% plus the secured overnight financing rate ("SOFR") administered by the Federal Reserve Bank of New York for a one-month tenor, subject to a 1.00% floor. See Note 14 to our consolidated financial statements included elsewhere in this Form 10-K. We may use interest rate cap derivatives, interest rate swaps or other interest rate hedging instruments to economically hedge and manage interest rate risk with respect to our variable floating rate debt. As of December 31, 2022, the annual interest rate was 13.02% and the outstanding balance of the Tranche 1 Notes was $75.0 million. Assuming no change in the outstanding borrowings under the Note Purchase Agreement, we estimate that a hypothetical 1% increase in the SOFR would increase our annual interest expense by approximately $0.8 million as of December 31, 2022.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
FOR THE YEARS ENDED DECEMBER 31, 2022 AND 2021
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of MeiraGTx Holdings plc and Subsidiaries

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of MeiraGTx Holdings plc and Subsidiaries (the "Company") as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, shareholders' equity and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2016.

Jericho, New York
March 14, 2023

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share amounts)

	December 31, 2022	December 31, 2021
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 115,516	$ 137,703
Accounts receivable - related party	21,334	22,384
Prepaid expenses	8,133	8,102
Tax incentive receivable	7,689	12,634
Other current assets	1,667	2,420
Total Current Assets	154,339	183,243
Property, plant and equipment, net	109,266	75,860
Intangible assets, net	1,335	1,791
In-process research and development	742	783
Other assets	1,402	1,404
Equity method and other investments	6,326	6,656
Right-of-use assets - operating leases, net	20,109	22,782
Right-of-use assets - finance leases, net	24,718	27,645
TOTAL ASSETS	$ 318,237	$ 320,164
LIABILITIES AND SHAREHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Accounts payable	$ 16,616	$ 15,348
Accrued expenses	39,818	27,586
Lease obligations, current	3,884	3,374
Deferred revenue - related party, current	15,123	21,820
Other current liabilities	6,631	—
Total Current Liabilities	82,072	68,128
Deferred revenue - related party	27,436	43,046
Lease obligations	17,331	20,359
Asset retirement obligations	2,179	2,081
Deferred income tax liability	186	196
Note payable, net	71,033	—
Other long-term liabilities	262	953
TOTAL LIABILITIES	200,499	134,763
COMMITMENTS AND CONTINGENCIES (Note 15)		
SHAREHOLDERS' EQUITY:		
Ordinary Shares, $0.00003881 par value, 1,288,327,750 authorized, 48,477,209 and 44,548,925 shares issued and outstanding at December 31, 2022 and 2021, respectively	2	2
Capital in excess of par value	581,893	528,659
Accumulated other comprehensive income (loss)	6,047	(2,671)
Accumulated deficit	(470,204)	(340,589)
Total Shareholders' Equity	117,738	185,401
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY	$ 318,237	$ 320,164

See Notes to Consolidated Financial Statements

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share amounts)

	For the Years Ended December 31,	
	2022	2021
License revenue - related party	$ 15,920	$ 37,701
Operating expenses:		
General and administrative	46,550	43,765
Research and development	85,725	66,694
Total operating expenses	132,275	110,459
Loss from operations	(116,355)	(72,758)
Other non-operating income (expense):		
Foreign currency loss	(9,452)	(6,293)
Interest income	777	212
Interest expense	(4,946)	(288)
Fair value adjustments	361	(434)
Net loss	(129,615)	(79,561)
Other comprehensive income:		
Foreign currency translation gain	8,718	2,226
Comprehensive loss	$ (120,897)	$ (77,335)
Net loss	$ (129,615)	$ (79,561)
Basic and diluted net loss per ordinary share	$ (2.87)	$ (1.80)
Weighted-average number of ordinary shares outstanding	45,177,857	44,139,655

See Notes to Consolidated Financial Statements

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY
FOR THE YEARS ENDED DECEMBER 31, 2022 AND 2021
(in thousands, except share amounts)

	Ordinary Shares	Amount	Capital in Excess of Par Value	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Shareholders' Equity
Balance at December 31, 2020	44,189,150	$ 2	$ 504,482	$ (4,897)	$ (261,028)	$ 238,559
Share-based compensation activity	186,638	—	22,493	—	—	22,493
Issuance of shares in connection with equity method and other investments	75,000	—	1,165	—	—	1,165
Issuance of shares in connection with asset acquisitions	98,137	—	519	—	—	519
Other comprehensive income	—	—	—	2,226	—	2,226
Net loss for the year ended December 31, 2021	—	—	—	—	(79,561)	(79,561)
Balance at January 1, 2022	44,548,925	2	528,659	(2,671)	(340,589)	185,401
Share-based compensation activity	185,770	—	26,080	—	—	26,080
Warrants issued in connection with note payable	—	—	2,273	—	—	2,273
Issuance of shares in connection with private placement, net of issuance costs of $119	3,742,514	—	24,881	—	—	24,881
Other comprehensive income	—	—	—	8,718	—	8,718
Net loss for the period ended December 31, 2022	—	—	—	—	(129,615)	(129,615)
Balance at December 31, 2022	48,477,209	$ 2	$ 581,893	$ 6,047	$ (470,204)	$ 117,738

See Notes to Consolidated Financial Statements

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	For the Years Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (129,615)	$ (79,561)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share-based compensation expense	28,623	20,784
Foreign currency loss	9,452	6,293
Depreciation and amortization	8,723	7,873
Net change in right-of-use assets and liabilities	(153)	161
(Gain) loss on disposal of equipment, furniture and fixtures	—	56
Loss on equity method investment	—	9
Amortization of interest on asset retirement obligations	168	148
Amortization of debt discount	444	—
Issuance of shares in connection with license agreement	—	976
Issuance of shares in connection with asset acquisition	—	1,020
Fair value adjustments	(361)	434
(Increase) decrease in operating assets:		
Accounts receivable - related party	1,032	16,391
Prepaid expenses	(329)	(1,083)
Tax incentive receivable	4,139	310
Other current assets	519	2,161
Other assets	(173)	(457)
Increase (decrease) in operating liabilities:		
Accounts payable	3,737	13,347
Accrued expenses	12,610	8,118
Other current liabilities	4,006	(23)
Deferred revenue - related party	(15,920)	(7,487)
Net cash used in operating activities	(73,098)	(10,530)
Cash flows from investing activities:		
Purchase of property, plant and equipment	(44,963)	(46,351)
Payment for right-of-use asset	—	(8,866)
Equity method and other investments	—	(6,500)
Net cash used in investing activities	(44,963)	(61,717)
Cash flows from financing activities:		
Exercise of share options	231	1,709
Payments of withholdings on shares withheld for income taxes	(2,774)	—
Payments on lease obligations - financing leases	—	(1)
Proceeds from the issuance of ordinary shares	25,000	—
Proceeds from issuance of note payable	75,000	—
Payment of financing fees	(2,257)	—
Net cash provided by financing activities	95,200	1,708
Net decrease in cash and cash equivalents	(22,861)	(70,539)
Effect of exchange rate changes on cash	674	(1,278)
Cash and cash equivalents at beginning of the year	137,703	209,520
Cash and cash equivalents at end of the year	$ 115,516	$ 137,703
Supplemental disclosure of non-cash transactions:		
Issuance of shares in connection with equity method and other investments	$ —	$ 1,165
Fixed asset acquisition included in accounts payable and accrued expenses	$ 7,106	$ 7,178
Right-of-use assets obtained in exchange for lease liabilities	$ 1,793	$ 4,424
Asset retirement obligations incurred in connection with leases	$ 9	$ 120
Warrants issued in connection with note payable	$ 2,273	$ —
Issuance of shares in connection with asset acquisition	$ —	$ 519
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 329	$ 139

See Notes to Consolidated Financial Statements

1. Principal Business Activity

The Company

MeiraGTx Holdings plc and subsidiaries (the "Company" or "Meira Holdings"), an exempted company incorporated under the laws of the Cayman Islands, is a vertically integrated, clinical stage gene therapy company with six programs in clinical development and a broad pipeline of preclinical and research programs. The Company has core capabilities in viral vector design and optimization and gene therapy manufacturing, as well as a potentially transformative gene regulation platform technology that allows precise, dose responsive control of gene expression by oral small molecules with dynamic range that can exceed 5000-fold. Led by an experienced management team, the Company has taken a portfolio approach by licensing, acquiring and developing technologies that give depth across both product candidates and indications. The Company's initial focus is on three distinct areas of unmet medical need: ocular diseases, including inherited retinal diseases as well as large degenerative ocular diseases, neurodegenerative diseases and severe forms of xerostomia. Though initially focusing on the eye, central nervous system and salivary gland, the Company intends to expand its focus in the future to develop additional gene therapy treatments for patients suffering from a range of serious diseases. The Company also owns and operates a current good manufacturing practices, or cGMP, multi-product, multi-viral vector manufacturing facility in London, United Kingdom ("UK"), which includes fill and finish capabilities and can supply the Company's clinical and potential commercial material. Additionally, the Company expanded its manufacturing and supply chain capabilities by acquiring a second, large scale cGMP viral vector manufacturing facility and its first cGMP plasmid and DNA production facility in Shannon, Ireland. The Company completed the acquisition of these facilities in January 2021.

Acquisition

On October 4, 2021, the Company acquired Bullseye Therapeutics, Inc. ("Bullseye"), a company engaged in developing mechanisms to deliver retinal drugs and gene therapies to the eye. Bullseye was renamed MeiraGTx Therapeutics, Inc.

This acquisition is part of the Company's continuing efforts to expand its focus to develop additional gene therapy treatments for patients suffering from a range of serious diseases. (See Note 3 for additional information).

Basis of Presentation

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

Liquidity

The Company has not yet achieved profitable operations. There is no assurance that profitable operations, if ever achieved, could be sustained on a continuing basis. In addition, development activities, clinical and preclinical testing, and commercialization of the Company's product candidates will require significant additional financing. The Company's accumulated deficit at December 31, 2022 totaled $470.2 million, and management expects to incur substantial losses in future periods. The success of the Company is subject to certain risks and uncertainties, including among others, uncertainty of product development; competition in the Company's field of use; uncertainty of capital availability; uncertainty in the Company's ability to enter into agreements with collaborative partners; expanding and protecting the Company's intellectual property portfolio; dependence on third parties; dependence on key personnel; the COVID-19 pandemic and mitigation measures. For the year ended December 31, 2022, the Company used $73.1 million in cash flows from operations and there are no assurances that the Company will

generate positive cash flows in the future. Additionally, there are no assurances that the Company will be successful in obtaining an adequate level of financing for the development and commercialization of its product candidates.

As of December 31, 2022, the Company had cash and cash equivalents in the amount of $115.5 million, which consisted of depository and money market accounts held at large international banks. On January 30, 2019, the Company entered into a collaboration, option and license agreement with Janssen Pharmaceuticals, Inc. ("Janssen"), one of the Janssen Pharmaceuticals Companies of Johnson & Johnson (the "Collaboration Agreement"), for the research, development and commercialization of gene therapies for the treatment of inherited retinal diseases ("IRD"). Under the terms of the Collaboration Agreement, the Company received an upfront payment of $100.0 million in March 2019 and a $30.0 million milestone payment in December 2021. The Company also receives funding for certain research, manufacturing, clinical development and commercialization costs, potential additional milestone payments upon the achievement of such milestones and royalties on future net sales of products. The Company estimates that its cash and cash equivalents on hand and accounts receivable – related party at December 31, 2022 will be sufficient to cover its expenses for at least the next twelve months from the date of issuance of these consolidated financial statements.

Risks and Uncertainties

The Company operates in an industry that is subject to intense competition, government regulation and rapid technological change. The Company's operations are subject to significant risk and uncertainties including financial, operational, technological, regulatory and other risks, including the potential risk of business failure.

There are also many uncertainties regarding the pandemic caused by the novel coronavirus, or COVID-19, and the Company continues to monitor the impact of the pandemic on all aspects of its business, including how the pandemic will impact its financial condition, liquidity, operations, clinical studies, employees, vendors, and industry. While the pandemic did not materially affect the Company's financial results and business operations in the year ended December 31, 2022 and 2021, the Company is unable to predict the impact that COVID-19 will have on its financial position and operating results in future periods due to numerous uncertainties. The Company will continue to assess the evolving impact of the COVID-19 pandemic and will make adjustments to its operations as necessary.

The Company's capital resources and operations to date have been funded primarily with the proceeds from the Collaboration Agreement and private and public equity offerings, as well as the proceeds from the debt financing described in Note 14. In the future, the Company may seek to raise additional capital through equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources to enable it to complete the development and potential commercialization of its product candidates. The COVID-19 outbreak and mitigation measures also have had, and may continue to have, an adverse impact on global economic conditions, which could have an adverse effect on the Company's ability to raise capital when needed.

2. Summary of Significant Accounting Policies

Consolidation

The accompanying consolidated financial statements include the accounts of Meira Holdings and its wholly owned subsidiaries:

MeiraGTx Limited, a limited company incorporated under the laws of England and Wales;
MeiraGTx, LLC, a Delaware limited liability company ("Meira LLC");
MeiraGTx UK II Limited, a limited company incorporated under the laws of England and Wales ("Meira UK II");

MeiraGTx Ireland DAC, a designated activity company incorporated under the laws of Ireland ("Meira Ireland");
MeiraGTx Netherlands B.V., a private company with limited liability incorporated under the laws of the Netherlands ("Meira Netherlands");
MeiraGTx Belgium, a private company with limited liability incorporated under the laws of Belgium ("Meira Belgium");
BRI-Alzan, Inc., a Delaware corporation ("BRI-Alzan");
MeiraGTx Bio Inc., a Delaware corporation ("Meira Bio");
MeiraGTx B.V., a private company with limited liability incorporated under the laws of the Netherlands ("Meira B.V.");
MeiraGTx Neurosciences, Inc., a Delaware corporation ("Meira Neuro");
MeiraGTx Therapeutics, Inc., a Delaware corporation ("Meira Therapeutics"); and
MeiraGTx UK Limited, a limited company incorporated under the laws of England and Wales ("Meira UK").

All intercompany balances and transactions between the consolidated companies have been eliminated in consolidation.

Use of Estimates

Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these consolidated financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. In preparing these consolidated financial statements, management used significant estimates in the following areas, among others: collaboration revenue, the accounting for research and development costs, share-based compensation, leases, asset retirement obligations, fair value of financial instruments and tax incentive receivable.

Additionally, the Company has made estimates of the impact of the COVID-19 pandemic within the consolidated financial statements and there may be changes to those estimates in future periods. Actual results may differ from these estimates.

Cash and Cash Equivalents

The Company considers all highly liquid instruments with an original maturity of 90 days or less at the time of purchase to be cash equivalents. Cash and cash equivalents consist of checking and money market accounts held at large international banks that are readily convertible into cash.

Financial Instruments

The carrying value of accounts receivable-related party, tax incentive receivable, other current assets, and accounts payable reported in the consolidated balance sheets equal or approximate fair value due to their short maturities.

Tax Incentive Receivable

Meira UK II is eligible to participate in a UK research and development tax incentive programs under which it is eligible to receive a cash refund from His Majesty's Revenue & Customs ("HMRC") for a percentage of the qualified research and development costs expended by Meira UK II under the small and medium sized enterprises ("SME") program and the research and development expenditures credit ("RDEC") program. The SME cash refund is available to companies with less than 500 employees and annual aggregate revenue of less than 100.0 million euros or total aggregate assets less than 86.0 million euros during the reimbursable period. The Company's estimate of the amount of cash refund it expects to receive related to the SME and RDEC programs is included in tax incentive receivable in the accompanying consolidated balance sheets and such amounts are recorded as a reduction of research and development expense in the statements of operations. During the years ended December 31, 2022 and 2021, the Company recorded reductions to research and development expenses of $6.8 million and $5.4 million, respectively.

In addition, the Company incurs Value Added Tax ("VAT") on services provided by UK and EU vendors, which it is entitled to reclaim. The Company's estimate of the amount of cash refund it expects to receive related to VAT was $1.1 million and $1.9 million as of December 31, 2022 and 2021, respectively, which is included in other current assets in the accompanying consolidated balance sheets.

Fair Value Measurements

Fair value is defined as the price that would be received upon sale of an asset or paid upon transfer of a liability in an orderly transaction between market participants at the measurement date and in the principal or most advantageous market for that asset or liability. The fair value should be calculated based on assumptions that market participants would use in pricing the asset or liability, not on assumptions specific to the entity. In addition, the fair value of liabilities should include consideration of non-performance risk including the Company's own credit risk.

The Company follows ASC Topic 820, *Fair Value Measurements and Disclosures*, or ASC 820, for application to financial assets and liabilities. In addition to defining fair value, the standard expands the disclosure requirements around fair value and establishes a fair value hierarchy for valuation inputs. The hierarchy prioritizes the inputs into three levels based on the extent to which inputs used in measuring fair value are observable in the market. Each fair value measurement is reported in one of the three levels which are determined by the lowest level input that is significant to the fair value measurement in its entirety. These levels are:

- Level 1: Observable inputs such as quoted prices in active markets for identical assets the reporting entity has the ability to access as of the measurement date;

- Level 2: Inputs, other than the quoted prices in active markets, that are observable either directly or indirectly; and

- Level 3: Unobservable inputs in which there is little or no market data, which require the reporting entity to develop its own assumptions.

The table below represents the values of the Company's financial assets and liabilities that are required to be measured at fair value on a recurring basis (in thousands):

		Fair Value Measurement Using:		
Description	December 31, 2022	Significant Observable Inputs (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable (Level 3)
Cash equivalents	$ 57,336	$ 57,336	$ —	$ —
Other long-term liabilities	$ 262	$ 262	$ —	$ —

		Fair Value Measurement Using:		
Description	December 31, 2021	Significant Observable Inputs (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable (Level 3)
Cash equivalents	$ 66,585	$ 66,585	$ —	$ —
Other long-term liabilities	$ 953	$ 953	$ —	$ —

Equity Method and Other Investments

The Company accounts for equity investments under the equity method of accounting when the requirements for consolidation are not met, and the Company has significant influence over the operations of the investee. Equity method investments are initially recorded at cost and subsequently adjusted for the Company's share of net income or loss and cash contributions and distributions and are included in equity method and other investments in the accompanying consolidated balance sheets. Equity investments that do not result in consolidation and are not accounted for under the equity method are measured at fair value, with any changes in fair value recognized in net income (loss). For any such investments that do not have readily determinable fair values, the Company elects the measurement alternative to measure the investments at cost minus impairment, if any, plus or minus changes resulting from observable price changes in orderly transactions for the identical or a similar investment of the same issuer. Equity method investments are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount may not be recoverable. If it is determined that a loss in value of the equity method investment is other than temporary, an impairment loss is measured based on the excess of the carrying amount of an investment over its estimated fair value. Impairment analyses are based on current plans, intended holding periods, and available information at the time the analysis is prepared.

Concentrations of Credit Risk

The Company maintains its cash and cash equivalents primarily in depository and money market accounts within two large financial institutions in the United States and one large financial institution in the United Kingdom and Ireland. Cash balances deposited at these major financial banking institutions exceed the insured limit. The Company has not experienced any losses on its bank deposits and believes these deposits do not expose the Company to any significant credit risk.

Intangible Assets

Intangible assets consist of purchased rights to licensed technology as it relates to the Company's manufacturing processes and has future alternative use in the Company's operations. The licensed technology is being amortized on a straight-line basis over 7 years, which represents the estimated periods of benefit and the expected pattern of consumption (see Note 7).

Property, Plant and Equipment, Net

Property, plant and equipment are stated at cost, net of accumulated depreciation. Depreciation is calculated using the straight-line method over the estimated useful lives of the respective assets. Leasehold improvements are depreciated over the lesser of their useful lives or the term of the lease (see Note 6).

The estimated useful lives of the asset categories are as follows:

Asset Category	Useful Lives
Computer and office equipment	3 years
Laboratory equipment	5 years
Manufacturing equipment	7 years
Furniture and fixtures	5 years
Leasehold improvements	lesser of useful life or remaining term of lease

Expenditures for leasehold improvements are capitalized, and expenditures for maintenance and repairs are expensed to operations as incurred.

ASC Topic 360, *Property, Plant and Equipment*, addresses the financial accounting and reporting for impairment or disposal of long-lived assets. The Company reviews the recorded values of long-lived assets for impairment whenever events or changes in business circumstances indicate that the carrying amount of an asset or group of assets may not be fully recoverable. The Company did not record any material impairment charges in 2022 or 2021.

Leases

The Company accounts for leases in accordance with ASC 842. The Company determines if an arrangement is a lease at contract inception. A lease exists when a contract conveys the right to control the use of identified property, plant, or equipment for a period of time in exchange for consideration. The definition of a lease embodies two conditions: (1) there is an identified asset in the contract that is land or a depreciable asset (i.e., property, plant, and equipment), and (2) the Company has the right to control the use of the identified asset. The Company accounts for the lease and non-lease components as a single lease component.

From time to time the Company enters into direct financing lease arrangements that include a lessee obligation to purchase the leased asset at the end of the lease term, a bargain purchase option, or provides for minimum lease payments with a present value of 90% or more of the fair value of the leased asset at the date of lease inception.

Operating leases where the Company is the lessee are included in right-of-use ("ROU") assets – operating leases and lease obligations are included on the Company's consolidated balance sheets. The lease obligations are initially and subsequently measured at the present value of the unpaid lease payments at the lease commencement date and subsequent reporting periods.

Finance leases where the Company is the lessee are included in ROU assets – finance leases, net and lease obligations on the Company's consolidated balance sheets. The lease obligations are initially measured in the same manner as for operating leases and are subsequently measured at amortized cost using the effective interest method.

Key estimates and judgments include how the Company determined (1) the discount rate used to discount the unpaid lease payments to present value, (2) lease term and (3) lease payments.

ASC 842 requires a lessee to discount its unpaid lease payments using the interest rate implicit in the lease or, if that rate cannot be readily determined, its incremental borrowing rate. As most of the Company's leases where it is the

lessee do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at commencement date in determining the present value of lease payments. The Company's incremental borrowing rate for a lease is the rate of interest it would have to pay on a collateralized basis to borrow an amount equal to the lease payments under similar terms. The Company uses the implicit rate when readily determinable.

The lease term for all of the Company's leases includes the non-cancellable period of the lease plus any additional periods covered by either a lessee option to extend (or not to terminate) the lease that is reasonably certain to be exercised, or an option to extend (or not to terminate) the lease controlled by the lessor.

The ROU asset is initially measured at cost, which comprises the initial amount of the lease liability adjusted for lease payments made at or before the lease commencement date less any lease incentives received.

For operating leases, the ROU asset is subsequently measured throughout the lease term at the carrying amount of the lease liability, minus any accrued lease payments, less the unamortized balance of lease incentives received. Lease expense for lease payments is recognized on a straight-line basis over the lease term.

For finance leases, the ROU asset is subsequently amortized using the straight-line method from the lease commencement date to the earlier of the end of its useful life or the end of the lease term unless the lease transfers ownership of the underlying asset, or the Company is reasonably certain to exercise an option to purchase the underlying asset. In those cases, the ROU asset is amortized over the useful life of the underlying asset. Amortization of the ROU asset is recognized and presented separately from interest expense on the lease liability.

The Company has elected not to recognize ROU assets and lease liabilities for all short-term leases that have a lease term of 12 months or less at lease commencement. Lease payments associated with short-term leases are recognized as an expense on a straight-line basis over the lease term.

Asset Retirement Obligations

Accounting for asset retirement obligations requires legal obligations associated with the retirement of long-lived assets to be recognized at fair value when incurred and capitalized as part of the related long-lived asset. In the absence of quoted market prices, the Company estimates the fair value of its asset retirement obligations using Level 3 present value techniques, in which estimates of future cash flows associated with retirement activities are discounted using a credit-adjusted risk-free rate. Asset retirement obligations currently reported on the Company's consolidated balance sheets were measured during a period of historically low interest rates. The impact on measurements of new asset retirement obligations using different rates in the future may be significant.

The Company uses estimates to determine the asset retirement obligations at the end of the lease term and discounts such asset retirement obligations using an estimated discount rate. Interest on the discounted asset retirement obligation is amortized over the term of the lease using the effective interest method and is recorded as interest expense in the consolidated statements of operations and comprehensive loss.

The change in asset retirement obligations is as follows (in thousands):

	For the Years Ended December 31,	
	2022	2021
Balance at beginning of period	$ 2,081	$ 1,814
Additional asset retirement obligations during the period	9	120
Amortization of interest	168	148
Effects of exchange rate changes	(79)	(1)
Balance at end of period	$ 2,179	$ 2,081

Share-Based Compensation Expense

Options

The Company grants share options to employees, non-employee members of the Company's board of directors and non-employee consultants as compensation for services performed. Employee and non-employee members of the board of directors' awards of share-based compensation are accounted for in accordance with ASC 718, *Compensation – Stock Compensation,* or ASC 718. ASC 718 requires all share-based payments to employees and non-employee directors, including grants of share options, to be recognized in the consolidated statement of operations and comprehensive loss based on their grant date fair values. The grant date fair value of share options is estimated using the Black-Scholes option valuation model.

Using this model, fair value is calculated based on assumptions with respect to (i) the fair value of the Company's ordinary shares on the grant date; (ii) expected volatility of the Company's ordinary share price, (iii) the periods of time over which the optionees are expected to hold their options prior to exercise (expected term), (iv) expected dividend yield on the Company's ordinary shares, and (v) risk-free interest rates.

The assumptions underlying these valuations represented management's best estimate, which involved inherent uncertainties and the application of management's judgment. As a result, if the Company had used different assumptions or estimates, the fair value of its ordinary shares and its share-based compensation expense could have been materially different.

The fair value of ordinary shares after the Company's IPO was determined based upon the closing share price on the date of grant.

Since the Company's ordinary shares had not been traded on a public exchange prior to the Company's IPO and have only been traded on a public exchange for a short period of time since the Company's IPO, the Company believes that it does not have sufficient company-specific information available to determine the expected term based on its historical data. As a result, the expected term of share options granted to the optionees is determined using the average of the vesting period and contractual life of the option, an accepted method for the Company's option grants under the Securities and Exchange Commission's ("SEC") Staff Accounting Bulletin No. 107 and No. 110, *Share-Based Payment.*

Similarly, the Company believes that its future volatility could differ materially during the expected term from the volatility that would be calculated from its historical share prices to date. Consequently, expected volatility is based on an analysis of guideline companies and the Company's own volatility in accordance with ASC 718. The expected dividend yield is zero as the Company has never paid dividends and does not currently anticipate paying any in the foreseeable future. Risk-free interest rates are based on quoted U.S. Treasury rates for securities with maturities approximating the option's expected term.

Restricted Share Units

The Company grants restricted share units ("RSUs") to employees, non-employee members of the Company's board of directors and non-employee consultants as compensation for services performed. Awards of RSUs are accounted for in accordance with ASC 718, *Compensation – Stock Compensation,* or ASC 718. ASC 718 requires all share-based payments to employees, non-employee members of the Company's board of directors and non-employee consultants, including grants of RSUs, to be recognized in the consolidated statement of operations and comprehensive loss based on their grant date fair values. The grant date fair value of RSUs is determined using the closing market price of the Company's ordinary shares on the date of grant.

Collaboration Arrangements

The Company evaluates its collaborative arrangements pursuant to ASC 808, *Collaborative Arrangements* ("ASC 808") and ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). The Company considers the nature and contractual terms of collaborative arrangements and assesses whether the arrangement involves a joint operating activity pursuant to which the Company is an active participant and is exposed to significant risks and rewards with respect to the arrangement. If the Company is an active participant and is exposed to significant risks and rewards with respect to the arrangement, the Company accounts for the arrangement as a collaboration under ASC 808. To date, the Company has entered into two separate collaboration agreements, both of which are with Janssen, which were determined to be within the scope of ASC 808.

ASC 808 does not address recognition or measurement matters related to collaborative arrangements. Payments between participants pursuant to a collaborative arrangement that are within the scope of other authoritative accounting literature on income statement classification are accounted for using the relevant provisions of that literature. If the payments are not within the scope of other authoritative accounting literature, the income statement classification for the payments is based on an analogy to authoritative accounting literature or if there is no appropriate analogy, a reasonable, rational and consistently applied accounting policy election. Payments received from a collaboration partner to which this policy applies may include upfront payments in respect of a license of intellectual property, development and commercialization-based milestones, and royalties.

Refer to the discussion in Note 12 for further information related to the accounting for the Collaboration Agreement.

Revenue Recognition

Arrangements with collaborators may include licenses to intellectual property, research and development services, manufacturing services for clinical and commercial supply, and participation on joint steering committees. The Company evaluates the promised goods or services to determine which promises, or group of promises, represent performance obligations. In contemplation of whether a promised good or service meets the criteria required of a performance obligation, the Company considers the stage of development of the underlying intellectual property, the capabilities and expertise of the customer relative to the underlying intellectual property, and whether the promised goods or services are integral to or dependent on other promises in the contract. When accounting for an arrangement that contains multiple performance obligations, the Company must develop judgmental assumptions, which may include market conditions, reimbursement rates for personnel costs, development timelines and probabilities of regulatory success to determine the stand-alone selling price for each performance obligation identified in the contract.

When the Company concludes that a contract should be accounted for as a combined performance obligation and recognized over time, the Company must then determine the period over which revenue should be recognized and the method by which to measure revenue. The Company generally recognizes revenue using a cost-based input method.

The Collaboration Agreement with Janssen is accounted for under ASC 808, however, as ASC 808 does not address recognition or measurement matters such as determining the appropriate unit of accounting or when the recognition criteria are met, the Company accounts for the consideration received from Janssen in accordance with ASC 606. In accordance with ASC 606, the Company recognizes revenue when its customer or collaborator obtains control of promised goods or services, in an amount that reflects the consideration which the Company expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, it 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;

iv. allocate the transaction price to the performance obligations within the contract; and

v. recognize revenue when (or as) the entity satisfies a performance obligation.

The Company only applies the five-step model to contracts when it determines that it is probable it will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer.

At contract inception, once the contract is determined to be by analogy within the scope of ASC 606, the Company assesses the goods or services promised within the contract to determine whether each promised good or service is a performance obligation. The promised goods or services in the Company's arrangements typically consist of a license to the Company's intellectual property and research, development and manufacturing services. The Company may provide options to additional items in such arrangements, which are accounted for as separate contracts when the customer elects to exercise such options, unless the option provides a material right to the customer. Performance obligations are promises in a contract to transfer a distinct good or service to the customer that (i) the customer can benefit from on its own or together with other readily available resources, and (ii) is separately identifiable from other promises in the contract. Goods or services that are not individually distinct performance obligations are combined with other promised goods or services until such combined group of promises meet the requirements of a performance obligation.

The Company determines transaction price based on the amount of consideration the Company expects to receive for transferring the promised goods or services in the contract. Consideration may be fixed, variable, or a combination of both. At contract inception for arrangements that include variable consideration, the Company estimates the probability and extent of consideration it expects to receive under the contract utilizing either the most likely amount method or expected amount method, whichever best estimates the amount expected to be received. The Company then considers any constraints on the variable consideration and includes in the transaction price variable consideration to the extent it is deemed probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

The Company then allocates the transaction price to each performance obligation based on the relative standalone selling price and recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) control is transferred to the customer and the performance obligation is satisfied. For performance obligations which consist of licenses and other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

The Company records amounts as accounts receivable when the right to consideration is deemed unconditional. When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded as deferred revenue.

Amounts received prior to satisfying the revenue recognition criteria are recognized as deferred revenue in the Company's consolidated balance sheet. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue – related party, current. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue – related party.

The Company's collaboration revenue arrangements include the following:

Up-front License Fees: If a license is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from nonrefundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone Payments: At the inception of an agreement that includes research and development milestone payments, the Company evaluates each milestone to determine when and how much of the milestone to include in the transaction price. The Company first estimates the amount of the milestone payment that the Company could receive using either the expected value or the most likely amount approach. The Company primarily uses the most likely amount approach as that approach is generally most predictive for milestone payments with a binary outcome. Then, the Company considers whether any portion of that estimated amount is subject to the variable consideration constraint (that is, whether it is probable that a significant reversal of cumulative revenue would not occur upon resolution of the uncertainty.) The Company updates the estimate of variable consideration included in the transaction price at each reporting date which includes updating the assessment of the likely amount of consideration and the application of the constraint to reflect current facts and circumstances.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on a level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company will recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any revenue related to sales-based royalties or milestone payments based on the level of sales.

Research and Development Services: The Company is incurring research and development costs, with Janssen responsible for up to 100% of the costs, depending on the type of research and development services being performed. The Company records costs associated with the development activities as research and development expenses in the consolidated statement of operations and comprehensive loss consistent with ASC 730, *Research and Development*. The reimbursement of the research and development costs by Janssen is representative of the joint risk sharing nature of the arrangement. The Company considered the guidance in ASC 808 and recognizes the payments received from Janssen as a reduction to research and development expense when the related costs are incurred.

Research and Development

Research and development costs are charged to expense as incurred. These costs include, but are not limited to, employee-related expenses, including salaries, benefits and travel of the Company's research and development

personnel; expenses incurred under agreements with contract research organizations and investigative sites that conduct clinical and preclinical studies and for the drug product for the clinical studies and preclinical activities; facilities; supplies; rent, insurance, certain legal fees, share-based compensation, depreciation, other costs associated with clinical and preclinical activities and regulatory operations and acquisition of in process research and development write-offs. Research funding under collaboration agreements and refundable research and development credits / tax credits are recorded as an offset to these costs.

Costs for certain development activities, such as Company funded outside research programs, are recognized based on an evaluation of the progress to completion of specific tasks with respect to their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the consolidated financial statements as prepaid or accrued research and development expenses, as the case may be.

Foreign Currencies

The Company's consolidated financial statements are presented in U.S. dollars, the reporting currency of the Company. The financial position and results of operations of Meira UK II, Meira Ireland, Meira Netherlands, Meira Belgium and Meira B.V. are measured using the foreign subsidiaries' local currency as the functional currency. These entities' cash accounts holding U.S. dollars are remeasured based upon the exchange rate at the date of remeasurement with the resulting gain or loss included in the consolidated statements of operations and comprehensive loss. Expenses of such subsidiaries have been translated into U.S. dollars at average exchange rates prevailing during the period. Assets and liabilities have been translated at the rates of exchange on the consolidated balance sheet dates. The resulting translation gain and loss adjustments are recorded directly as a separate component of shareholders' equity and as other comprehensive loss on the consolidated statements of operations and comprehensive loss.

Income Taxes

Income taxes are recorded in accordance with ASC Topic 740, *Income Taxes*, or ASC 740, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Realization of net deferred tax assets is dependent on future taxable income. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some, or all, of the deferred tax assets will not be realized. Realization of net deferred tax assets is dependent on future taxable income (see Note 11).

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2022 and 2021, the Company recorded unrecognized tax positions of $0.9 and $0.7 million, respectively. No interest and penalties have been accrued relative to the unrecognized tax positions.

The Company is required to estimate income taxes in each of the jurisdictions in which it operates.

Net Loss per Ordinary Share

Basic net loss per ordinary share is computed by dividing net loss by the weighted average number of shares of the Company's ordinary shares outstanding during the period of computation. Diluted net loss per ordinary share is

computed similar to basic net loss per share except that the denominator is increased to include the number of additional ordinary shares that would have been outstanding if the ordinary share equivalents had been issued at the beginning of the year and if the additional ordinary shares were dilutive (treasury stock method) or the two-class method, whichever is more dilutive. For all periods presented, basic and diluted net loss per ordinary share are the same as any additional ordinary share equivalents would be anti-dilutive.

The following securities are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti-dilutive:

	December 31, 2022	December 31, 2021
Share options	6,858,409	5,924,690
Restricted share units	2,182,500	1,415,000
Warrants	700,000	—
Restricted ordinary shares subject to forfeiture	14,049	173,097
	9,754,958	7,512,787

Other Comprehensive Loss

Other comprehensive loss is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. The only component of other comprehensive loss impacting the Company is foreign currency translation.

Segment Information

Management has concluded it has a single reporting segment for purposes of reporting financial condition and results of operations.

The Company's license revenue, research funding and deferred revenue from its Collaboration Agreement are generated in the United Kingdom.

The following table summarizes long-lived assets by geographical area (in thousands):

	December 31, 2022	December 31, 2021
United States	$ 20,809	$ 23,636
United Kingdom	37,778	43,349
European Union	105,311	69,936
	$ 163,898	$ 136,921

Recent Accounting Pronouncements Not Yet Adopted

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*, which adds a new Topic 326 to the Codification and removes the thresholds that companies apply to measure credit losses on financial instruments measured at amortized cost, such as loans, receivables, and held-to-maturity debt securities. Under current GAAP, companies generally recognize credit losses when it is probable that the loss has been incurred. The revised guidance will remove all recognition thresholds and will require companies to recognize an allowance for credit losses for the difference between the amortized cost basis of a financial instrument and the amount of amortized cost that the company expects to collect over the instrument's contractual life. ASU 2016-13 also amends the credit loss measurement guidance for available-for-sale debt securities and beneficial interests in securitized financial assets. The guidance is applicable for fiscal years beginning after December 15, 2019 and interim periods within those years, however, the FASB extended the

effective date for smaller reporting companies to fiscal years beginning after December 15, 2022. The Company does not believe that the adoption of this standard will have a significant impact on its related disclosures.

3. Acquisition

Bullseye Therapeutics, Inc.

On October 4, 2021 (the "Bullseye Closing Date"), the Company acquired the stock of Bullseye, a company engaged in developing mechanisms to deliver retinal drugs and gene therapies to the eye. As a result, Bullseye is a wholly-owned subsidiary of the Company and was renamed MeiraGTx Therapeutics, Inc.

In connection with the acquisition of Bullseye, the consideration to Bullseye's selling stockholders consisted of an aggregate of 80,276 of the Company's ordinary shares of which (i) 12,040 ordinary shares were issued on the Bullseye Closing Date, (ii) 28,097 restricted ordinary shares were issued on the Bullseye Closing Date, with 50% of such restricted ordinary shares scheduled to vest on each of the first and second anniversaries of the Bullseye Closing Date, and (iii) 40,139 ordinary shares will be issued 18 months following the Bullseye Closing Date, provided that the shares described in clauses (ii) and (iii) are subject to certain indemnification claims under the Bullseye Merger Agreement. The Company also assumed $0.5 million of Bullseye's liabilities ("Assumed Liabilities"). Total consideration of $1.5 million was based on the closing price of the Company's ordinary shares of $13.31 per share on October 1, 2021, plus the Assumed Liabilities.

The Company determined this transaction represented an asset acquisition as substantially all of the value was in the intellectual property as defined by ASC 805, *Business Combinations* ("ASC 805"). The asset acquisition of in-process research and development was recorded at a fair value of $1.5 million as of October 4, 2021. The acquired in process research and development was immediately charged to research and development expense in the consolidated statement of operations and comprehensive loss as of the acquisition date since the Company determined that there was no alternative future use for these assets.

The 40,139 ordinary shares that are to be issued 18 months following the Bullseye Closing Date were recorded as a liability at a fair value of $0.5 million on the Bullseye Closing Date. At December 31, 2022 and 2021, the liability was revalued to $0.3 million and $1.0 million, respectively, based upon the closing price of the Company's ordinary shares of $6.52 and $23.74 per share on December 31, 2022 and 2021, respectively. The $0.7 million and $0.5 million change in fair value was recorded as a fair value adjustment for the years ended December 31, 2022 and 2021, respectively. The change in fair value was included as part of research and development expenses in the prior year, but for comparative purposes it has been presented as a fair value adjustment in the consolidated statements of operations and comprehensive loss.

4. Equity Method and Other Investments

The Company's investments consist of the following (in thousands):

		December 31, 2022		
Investee	Investment Type	Ownership Percentage	Carrying Value	Cost Basis
Visiogene LLC	Equity Method Investment	25 %	$ 5,156	$ 5,165
Other	Equity Investment	1.6 %	1,170	1,500
Total equity method and other investments			$ 6,326	$ 6,665

Visiogene LLC

On January 4, 2021, the Company and Visiogene LLC ("Visiogene") entered into a License and Investment Agreement ("Visiogene License Agreement") for an exclusive, worldwide license to certain of Visiogene's intellectual property relating to ocular gene therapy. Concurrently, the Company and Visiogene entered into a Preferred Unit Purchase Agreement ("Visiogene Unit Agreement") pursuant to which the Company purchased 3,000,000 Visiogene preferred units. In connection with the two Visiogene agreements, the Company paid $5.0 million in cash and issued to Visiogene 75,000 ordinary shares of the Company with a fair market value of $1.2 million based on the closing price of the Company's ordinary shares on the date of closing.

The Company accounted for the payments under the Visiogene License Agreement and Visiogene Unit Agreement as a basket transaction and allocated $1.0 million to the Visiogene License Agreement and the remaining $5.2 million was allocated to the Visiogene preferred units. The $1.0 million allocated to the Visiogene License Agreement was expensed as acquired in-process research and development as the Company determined there was no alternative future use. The Company accounts for this investment using the equity method of accounting.

During the years ended December 31, 2022 and 2021, the Company recorded de minimis research and development expenses related to the Company's share of Visiogene's losses.

Other Equity Investment

During the year ended December 31, 2022, the Company recognized a $0.3 million impairment due to the dilution of the Company's ownership percentage of the investment. The $0.3 million impairment was recorded as a fair value adjustment for the year ended December 31, 2022.

5. Prepaid Expenses

Prepaid expenses at December 31, 2022 and 2021 consist of the following (in thousands):

	December 31, 2022	December 31, 2021
Clinical trial costs	$ 3,411	$ 2,322
Research and development	1,220	991
Insurance	1,485	2,122
Dues and license fees	909	1,185
Facilities costs	539	455
Manufacturing costs	347	624
Other	222	403
	$ 8,133	$ 8,102

6. Property, Plant and Equipment, net

Property, plant and equipment, net at December 31, 2022 and 2021 consist of the following (in thousands):

	December 31, 2022	December 31, 2021
Leasehold improvements	$ 91,053	$ 60,878
Manufacturing equipment	17,373	12,156
Laboratory equipment	13,804	10,868
Computer and office equipment	6,787	5,750
Furniture and fixtures	642	687
	129,659	90,339
Less: Accumulated depreciation	(20,393)	(14,479)
	$ 109,266	$ 75,860

In connection with certain operating leases, the Company has determined that it has asset retirement obligations in the aggregate amount of $3.9 million at the end of those leases. The Company discounted the asset retirement obligations using an 8% discount rate and recorded an asset retirement obligation in the aggregate amount of $1.8 million, which is included in leasehold improvements and is being amortized over the term of the respective leases.

Depreciation and amortization expense related to property, plant and equipment was $7.3 million and $6.3 million for the years ended December 31, 2022 and 2021, respectively.

7. Intangible Assets

In November 2020, the Company entered into a non-exclusive, royalty-free technology license agreement that required the Company to pay an upfront payment to the licensor of $2.1 million. The Company accounted for the transaction as an asset acquisition and recorded an intangible asset as it was determined to have alternative future uses in connection with the Company's manufacturing capabilities.

The following table presents the details of the Company's intangible assets as of December 31, 2022 and 2021 (in thousands):

	December 31, 2022	December 31, 2021
Licensed Technology	$ 1,900	$ 2,119
Less: Accumulated amortization	(565)	(328)
	$ 1,335	$ 1,791

The intangible asset is being amortized over a period of seven years. Amortization expense of $0.2 million and $0.3 million was recorded as a component of research and development expenses for the years ended December 31, 2022 and 2021, respectively.

As of December 31, 2022, the expected amortization expense for the next five years and thereafter is as follows (in thousands):

	Amortization Expense
2023	$ 272
2024	272
2025	272
2026	272
2027	247
Thereafter	—
Total amortization	$ 1,335

8. Accrued Expenses

Accrued expenses at December 31, 2022 and 2021 were comprised of the following (in thousands):

	December 31, 2022	December 31, 2021
Clinical trial costs	$ 13,041	$ 12,524
Compensation and benefits	9,600	6,029
Research and development	7,400	1,735
Manufacturing costs	4,326	2,889
Fixed assets	3,093	2,077
Professional fees	732	1,018
Consulting	694	858
Other	932	456
	$ 39,818	$ 27,586

9. Share-Based Compensation

Equity Incentive Plans

The Company's 2018 Incentive Award Plan and 2016 Equity Incentive Plan (collectively, the "Plans"), were adopted by the Company's board of directors and shareholders. Under the Plans, the Company has granted share options and restricted share units ("RSUs") to selected officers, employees, non-employee members of the Company's board of directors and non-employee consultants. The Company's board of directors or a committee thereof administers the Plans. Upon the adoption of the 2018 Incentive Award Plan, the Company ceased issuing awards under the 2016 Equity Incentive Plan. The number of shares available for issuance under the 2018 Incentive Award Plan are increased on January 1 of each calendar year beginning in 2019 and ending in and including 2028, by an amount equal to the lesser of (A) 4% of the ordinary shares outstanding on the final day of the immediately preceding calendar year and (B) a smaller number of shares determined by the Company's board of directors. Under the 2018 Incentive Award Plan the Company initially reserved up to 3,054,996 shares for issuance, which has been increased to 9,171,660 as of December 31, 2022. As of December 31, 2022, 843,802 shares remain available for future issuance. In January 2023, the number of shares available for issuance under the 2018 Incentive Award Plan increased by 1,939,088 shares. Also, in February 2023, the Company's board of directors approved up to 2,250,000 options and restricted share units to be granted to certain executives, employees and consultants, in each case, under the 2018 Incentive Award Plan.

Options

A summary of the Company's share option activity related to employees, non-employee members of the board of directors and non-employee consultants as of and for the years ended December 31, 2022 and 2021 is as follows (in thousands, except share and per share amounts):

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)
Outstanding at December 31, 2020	4,824,771	$ 11.85	
Granted	1,667,700	$ 15.53	
Exercised	(186,638)	$ 9.16	
Forfeited	(381,143)	$ 12.22	
Outstanding at December 31, 2021	5,924,690	$ 13.16	7.40 years
Granted	1,492,400	$ 18.54	
Exercised	(27,081)	$ 8.53	
Forfeited	(531,600)	$ 17.52	
Outstanding at December 31, 2022	6,858,409	$ 14.03	6.86 years
Options exercisable at December 31, 2022	4,547,271	$ 12.18	6.00 years
Aggregate intrinsic value of options outstanding as of December 31, 2022	$ 1,819		
Aggregate intrinsic value of options exercisable as of December 31, 2022	$ 1,810		

Options granted under the Plans have a maximum contractual term of ten years. Options granted generally vest 25% on the first anniversary of the date of grant and the balance ratably over the next 36 months. Options granted to directors when they join the board generally vest in 36 equal monthly installments following the date of grant, and annual options granted to directors generally vest on the earlier of the first anniversary of the date of grant or the day before the Company's next annual meeting of shareholders after the date of grant.

The total share-based compensation expense recorded in connection with the options was $16.1 million and $14.8 million, of which $5.7 million and $6.2 million was recorded as general and administrative expense and $10.4 million and $8.6 million was recorded as research and development expense during the years ended December 31, 2022 and 2021, respectively.

The total fair value of options vested during the years ended December 31, 2022 and 2021 was $16.2 million and $14.4 million, respectively.

The weighted average grant date fair value of options granted during the years ended December 31, 2022 and 2021 was $12.81 and $11.44, respectively. The grant date fair values of the share options granted were estimated using the Black-Scholes option valuation model with the following ranges of assumptions (see Note 2):

	2022	2021
Risk-free interest rate	1.56 - 4.23%	0.62 - 1.39%
Expected volatility	80%	90%
Expected dividend yield	0%	0%
Expected term (in years)	5.5 - 6.1	5.5 - 6.1

As of December 31, 2022, the total compensation expense relating to unvested options granted that had not yet been recognized was $24.7 million, which is expected to be recognized over a period of 4.0 years. The Company will issue shares upon exercise of options from ordinary shares reserved under the Plans.

Restricted Share Units

A summary of the Company's RSU activity related to employees, non-employee members of the board of directors and non-employee consultants for the years ended December 31, 2022 and 2021 is as follows:

	Number of Restricted Share Units	Weighted-Average Grant Date Fair Value
Outstanding at December 31, 2020	545,000	$ 20.02
Granted	870,000	$ 15.36
Vested	—	$ —
Forfeited	—	$ —
Outstanding at December 31, 2021	1,415,000	$ 17.16
Granted	1,180,000	$ 20.12
Vested	(397,500)	$ 18.40
Forfeited	(15,000)	$ 8.25
Outstanding at December 31, 2022	2,182,500	$ 18.59

RSUs granted generally vest 50% on the second anniversary of the date of grant and 25% on the third and fourth anniversaries of the date of grant. Annual RSUs granted to directors generally vest in a single installment on the earliest to occur of the first anniversary of the grant date or the day immediately prior to the date of the next annual meeting of the Company's shareholders occurring after the date of grant. The RSUs granted to the directors in June 2021 will be paid on or within 30 days after the date a director ceases to serve on the board. For RSUs granted in future years, the directors may elect whether to defer the payment of their annual RSU awards under the Deferred Compensation Plan for Non-Employee Directors, which was adopted by the board on December 17, 2021. The related share-based compensation expense, which is recognized ratably over the requisite service period, is included in general and administrative and research and development expenses, as applicable, in the consolidated statements of operations and comprehensive loss.

Total share-based compensation expense recorded in connection with the RSUs was $12.5 million and $6.0 million, of which $8.8 million and $4.9 million was recorded as general and administrative expense and $3.7 million and $1.1 million was recorded as research and development expense during the years ended December 31, 2022 and 2021, respectively.

As of December 31, 2022, the total compensation expense relating to unvested RSUs granted that had not yet been recognized was $26.9 million, which is expected to be recognized over a period of 3.0 years.

During the years ended December 31, 2022 and 2021 the Company recognized total share-based compensation expense in the accompanying consolidated statements of operations and comprehensive loss as follows (in thousands):

	Years Ended December 31,	
	2022	2021
Research and development	$ 14,165	$ 9,685
General and administrative	14,458	11,099
Total share-based compensation	$ 28,623	$ 20,784

The Company does not expect to realize any tax benefits from its share option activity or the recognition of share-based compensation expense because the Company currently has net operating losses and has a full valuation allowance against its deferred tax assets. Accordingly, no amounts related to excess tax benefits have been reported in cash flows from operations or cash flows from financing activities for the years ended December 31, 2022 and 2021.

10. Ordinary Shares

2022

Private Placement

On November 9, 2022, the Company entered into a securities purchase agreement with Johnson & Johnson Innovation – JJDC, Inc. ("JJDC"), the investment arm of Johnson & Johnson, pursuant to which the Company, in a private placement, agreed to issue and sell to JJDC an aggregate of 3,742,514 ordinary shares at a purchase price of $6.68 per share, for gross proceeds of approximately $25.0 million.

2021

Equity Method and Other Investments

As discussed in Note 3, on January 4, 2021, the Company issued 75,000 ordinary shares in connection with the Visiogene transaction in the amount of $1.2 million.

Acquisitions

As discussed in Note 3, on October 4, 2021 the Company issued 12,040 ordinary shares as well as 28,097 ordinary shares which are subject to vesting in connection with the Bullseye acquisition.

On October 9, 2021, the Company issued 58,000 holdback ordinary shares in connection with a previous acquisition.

11. Income Taxes

For the years ended December 31, 2022 and 2021, the Company recognized a tax benefit of $0.

As of December 31, 2022, the Company had U.S. federal and state net operating losses ("NOLs") and foreign carryforward tax losses which are available to reduce future taxable income of (in thousands):

	Federal	State/City
United Kingdom	$ 187,939	$ —
United States	$ 63,829	$ 64,405
Other	$ 22,274	$ —

The U.S. federal and state NOLs incurred prior to January 1, 2018 in the amount of approximately $1.0 million and $0.8 million, respectively, will begin to expire in 2036. The U.S. NOLs incurred after December 31, 2017 and the UK carryforward tax losses will be indefinitely carried forward. Also, as of December 31, 2022, the Company had orphan drug and research and development credits in the U.S. in the amount of $9.4 million which will begin to expire in 2036 and research and development credits of $2.4 million in the UK which can be carried forward indefinitely. The U.S. NOLs and UK carryforward tax losses may become subject to an annual limitation in the

event of certain cumulative changes in the ownership interest of significant shareholders, as defined under Section 382 of the Internal Revenue Code, as well as UK tax rules. This could limit the amount of NOLs and carryforward tax losses that the Company can utilize annually to offset future taxable income or tax liabilities. As of December 31, 2021, the Company had performed such an analysis and determined that there were no limitations in the UK. However, for U.S. purposes, the Company determined that a change of ownership occurred in April 2016 and again in June 2018. The Company is still in the process of determining the annual limitation on losses that occurred prior to June 2018.

The Company's pre-tax loss is as follows (in thousands):

	December 31, 2022	December 31, 2021
United Kingdom	$ (54,636)	$ (17,056)
United States	(54,513)	(49,223)
Other	(20,467)	(13,282)
	$ (129,616)	$ (79,561)

The Company is subject to the corporate tax rate in the UK as a limited UK corporation.

The following table summarizes a reconciliation of income tax benefit compared with the amounts at the UK statutory income tax rate (in thousands):

	December 31, 2022		December 31, 2021	
Statutory rate	(24,627)	19.00 %	(15,117)	19.00 %
Permanent differences - other	2,323	(1.79)%	934	(1.17)%
RTP and other adjustment	1,244	(0.96)%	(2,735)	3.44 %
State and local rate, net of federal tax	(5,660)	4.37 %	(5,850)	7.35 %
U.K. tax credit	2,296	(1.77)%	(1,464)	1.84 %
U.S. tax credit	(2,436)	1.88 %	(1,491)	1.87 %
Foreign tax rate differential	195	(0.15)%	(540)	0.68 %
UK rate change (25% & 19% at expected DTA turn)	(1,973)	1.52 %	(10,247)	12.88 %
US state rate change	(3)	0.00 %	(447)	0.56 %
Section 162(m) deferred adjustment	1,386	(1.07)%	—	0.00 %
Change in valuation allowance	27,255	(21.03)%	36,957	(46.45)%
Actual income tax benefit effective tax rate	—	0.00 %	—	0.00 %

The Expense/(Benefit) for income taxes from continuing operations consists of the following (in thousands):

	December 31, 2022	December 31, 2021
Current Tax Expense/(Benefit)		
United Kingdom	—	—
United States	—	—
Other	—	—
Total Current	—	—
Deferred Tax Expense/(Benefit)		
United Kingdom	(8,708)	(16,079)
United States	(17,466)	(17,369)
Other	219	(3,509)
Total Deferred	(25,955)	(36,957)
Change in Valuation Allowance	25,955	36,957
Total Income Tax Expense/(Benefit)	—	—

Deferred Tax Assets/(Liabilities) (in thousands):

	December 31, 2022	December 31, 2021
Deferred Tax Assets:		
Net operating loss carryforwards	$ 74,350	$ 74,007
Capitalized research and development	16,288	—
Share-based compensation	13,684	10,314
R&D credit	10,837	7,498
Lease liability	6,461	7,040
Other	3,745	1,481
Deferred tax assets	125,365	100,340
Deferred Tax Liabilities:		
Indefinite-lived intangibles and fixed assets	(186)	(196)
Depreciation	(2,935)	(3,339)
Right of use assets	(6,207)	(6,733)
Less: valuation allowance	(116,223)	(90,268)
Net deferred tax liability	$ (186)	$ (196)

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a full valuation allowance, after consideration of the reversal of the deferred tax liabilities for the ROU assets and fixed assets, against its deferred tax assets at December 31, 2022 and 2021 because the Company's management has determined that is it more likely than not that these assets will not be fully realized.

Changes to the UK corporation tax rates have been announced which will impact future accounting periods. Finance Act 2021 increases the UK corporation tax rate from 19% to 25% effective April 1, 2023 for companies with profits in excess of GBP 250,000. As the Company does not expect to be able to utilize its carryforward tax losses in the UK until after April 2023, the deferred tax has been calculated using a tax rate of 25%.

As of December 31, 2022 and 2021, the Company recorded unrecognized tax positions of $0.9 million and $0.7 million, respectively. The unrecognized tax positions are netted with deferred tax assets above with full valuation allowance. The changes to unrecognized tax positions for 2022 and 2021 were as follows (in thousands):

	December 31, 2022	December 31, 2021
Unrecognized tax benefits as of January 1	$ 666	$ 513
Gross increases/(decreases) related to current year	279	165
Gross increases/(decreases) related to prior years	(8)	(12)
Foreign currency translation	—	—
Unrecognized tax positions as of December 31	$ 937	$ 666

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022 and 2021, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statements of operations and comprehensive loss.

The Company files income tax returns in the United States, UK, various foreign jurisdictions and various U.S. state jurisdictions. In the U.S., all years remain subject to examination. The earliest year subject to examination in the UK is 2020.

MeiraGTx Holdings plc is a UK tax resident with no earnings in its foreign subsidiaries and the Company does not expect any temporary basis difference in its investment in these subsidiaries to reverse in the foreseeable future. Therefore, the Company has not recorded deferred taxes on the outside basis difference in its foreign subsidiaries. It is not probable to compute the amounts, if any.

12. Related Party Transactions

Collaboration and License Agreements

Janssen Pharmaceuticals, Inc.

On January 30, 2019, the Company entered into a Collaboration Agreement with Janssen for the research, development and commercialization of gene therapies for the treatment of IRD. Under the agreement, Janssen paid the Company a non-refundable upfront fee of $100.0 million. Janssen and the Company will collaborate to develop the Company's current clinical programs in retinitis pigmentosa and two genetic forms of achromatopsia and Janssen has the exclusive right to commercialize these three product candidates ("Clinical IRD Product Candidates") globally.

Pursuant to the Collaboration Agreement, the Company and Janssen also agreed on a research collaboration to develop a pipeline of preclinical inherited retinal disease gene therapy candidates ("Research IRD Product Candidates"). The parties will select and prioritize the Research IRD Product Candidates and Janssen has the right to opt-in for a fee for each of the specified targets (each an "Option Target") to obtain certain development, manufacturing and commercialization rights for the Research IRD Product Candidates.

Unless terminated earlier under certain termination clauses, the Collaboration Agreement will continue in effect, on a product-by-product and country-by-country basis, until such time as the royalty terms expire in such country. The Company has determined enforceable rights exist in the Collaboration Agreement as the termination clauses are substantive termination penalties by way of the non-refundable upfront fee and the reversion of any licensed intellectual property granted to Janssen upon the termination of the agreement.

On February 27, 2019, in connection with a private placement, the Company issued 2,898,550 ordinary shares to JJDC, the investment arm of Johnson & Johnson and owner of Janssen, on the same terms and conditions as the other investors in the offering. After the offering, JJDC became a related party. On November 9, 2022, the Company entered into a securities purchase agreement with JJDC, pursuant to which the Company, in a private placement, agreed to issue and sell to JJDC an aggregate of 3,742,514 ordinary shares at a purchase price of $6.68 per share, for gross proceeds of approximately $25.0 million.

Clinical IRD Product Candidates

Under the Collaboration Agreement, the Company and Janssen will jointly develop Clinical IRD Product Candidates to permit Janssen to commercialize such Clinical IRD Product Candidates under an exclusive license from the Company. In general, the Company will have the primary responsibility to develop each Clinical IRD Product Candidate in accordance with the development plan for each Clinical IRD Product Candidate, including where applicable, conducting any necessary research in order to submit the applicable regulatory filings to regulatory authorities. The Company will manufacture these products in its cGMP manufacturing facilities for both clinical and commercial supply. Janssen will pay 100% of the clinical and commercialization costs of the products and the Company is eligible to receive untiered 20% royalties on net sales of products and additional development and commercialization milestones up to $340.0 million. The Company received its first milestone payment of $30.0 million in December 2021.

Research IRD Product Candidates

Under the Collaboration Agreement, the Company and Janssen will collaborate to develop Research IRD Product Candidates, with Janssen paying for the majority of the research costs. Janssen has the right to exclusively license any product coming out of the collaboration at the time of an investigational new drug application for an additional fee for each Research IRD Product Candidate. Janssen will then pay 100% of the clinical and commercialization costs for these Research IRD Product Candidates and the Company will receive an untiered royalty on net sales in the high teens as well as development milestones for each Research IRD Product Candidate.

Revenue Recognition under the Collaboration Agreement

The Collaboration Agreement is accounted for under ASC 808, however, ASC 808 does not address recognition or measurement matters. Therefore, the Company will account for the recognition and measurement of consideration under ASC 606. In determining the appropriate amount of revenue to be recognized under ASC 606, the Company performed the following steps: (i) identified the promised goods or services in the contract; (ii) determined whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The Company evaluated the potential performance obligations in the contract, which included the exclusive license to Clinical IRD Product Candidates, the research, development and manufacturing services ("the services"), and the participation in various joint committees and determined that none of the performance obligations by themselves were distinct. Goods and services that are not distinct are bundled with other goods or services in the contract until a bundle of goods or services that is distinct is created. The services, when combined with the licenses, represent a bundle and should be accounted for as a single performance obligation due to the relevance of the services to the value of the early-stage license and the potential for the intellectual property to be significantly modified during the services period. The Company also evaluated whether or not the right to purchase exclusive option rights for specified Research IRD Product Candidates represents future performance obligations and concluded that these represent a separate buyer decision at market rates, rather than a material right performance obligation. As such, these options have been excluded from the initial allocation of transaction price and the Company will account for these options as separate contracts when and if Janssen elects to exercise the options.

Under ASC 606, the Company recognized collaboration revenue using the cost-to-cost input method, which it believes 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 combined performance obligation by the potential product candidate. Under this method, revenue is being recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. Under ASC 606, the estimated transaction price includes variable consideration subject to constraints. The Company does not include variable consideration to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will occur when any uncertainty associated with the variable consideration is resolved. The estimate of the Company's measure of progress and estimate of variable consideration to be included in the transaction price will be updated at each reporting date as a change in estimate. The amount related to the unsatisfied portion will be recognized as that portion is satisfied over time.

Under ASC 606 the Company accounts for (i) the licenses it conveyed with respect to the Clinical IRD Product Candidates and (ii) its obligations to perform services as a single performance obligation under the Collaboration Agreement with Janssen on a product candidate basis. Janssen's right to purchase exclusive options to obtain certain development, manufacturing and commercialization rights are accounted for separately as they do not represent material rights, based on the criteria of ASC 606. Upon the exercise of any purchased option by Janssen, the contract promises associated with an Option Target would use a separate cost-to-cost model for purposes of revenue recognition under ASC 606.

During the year ended December 31, 2019, the Company received a $100.0 million non-refundable upfront fee from Janssen and during the year ended December 31, 2021, the Company received a $30.0 million milestone payment. The Company allocated these amounts plus other variable consideration not subject to constraint to each identified performance obligation using a combination of methods allowable under ASC 606. The Company applies the practical expedient in Topic 606 and does not include disclosures regarding amounts for variable consideration allocated to wholly-unsatisfied performance obligations or wholly-unsatisfied distinct goods that form part of a single performance obligation, if any. This variable consideration includes expected reimbursement of research and development costs.

During the years ended December 31, 2022 and 2021, the Company recognized $15.9 million and $37.7 million, respectively, of the deferred revenue – related party as license revenue.

The Company also recognized $73.3 million and $69.0 million during the years ended December 31, 2022 and 2021, respectively, related to the reimbursement of research and development expenses.

As of December 31, 2022, the Company expects to recognize the remaining $42.6 million in deferred revenue associated with the non-refundable upfront fee and milestone payment over the estimated research and development period using the cost-to-cost input method over an estimated period of approximately 2.9 years.

A summary of the deferred revenue recognition is as follows (in thousands):

Deferred revenue at December 31, 2020	$	72,842
Milestone payment from Janssen		30,000
Deferred revenue recognized as license revenue during the year ended December 31, 2021		(37,701)
Effects of exchange rate changes		(275)
Deferred revenue at December 31, 2021		64,866
Deferred revenue recognized as license revenue during the year ended December 31, 2022		(15,920)
Effects of exchange rate changes		(6,387)
Deferred revenue at December 31, 2022	$	42,559

Debt Financing

On August 2, 2022 the Company, as borrower, and Meira UK II and Meira Ireland, as guarantors (the "Subsidiary Guarantors"), entered into a senior secured financing arrangement (the "Financing Agreement") by and among the Company, the Subsidiary Guarantors, the lenders and other parties from time to time party thereto and Perceptive Credit Holdings III, LP, as administrative agent and lender ("Perceptive"). On December 19, 2022, the Financing Agreement was converted to a note purchase agreement (the "Note Purchase Agreement") between the same parties and under substantially the same terms and conditions as the Financing Agreement, subject to certain customary note constitution terms. Perceptive Advisors, LLC, an affiliate of Perceptive, is a 15.6% holder of the ordinary shares of the Company. Additionally, Ellen Hukkelhoven, Ph.D., a director of the Company, is an employee of Perceptive Advisors, LLC. Refer to the discussion in Note 14 for further information related to the accounting for the debt financing.

Leases

ARE Vivarium Lease

Effective May 1, 2019, the Company entered into an operating lease for vivarium space with ARE East River Science Park, LLC ("ARE"), which was subsequently amended to add additional space within the vivarium. ARE is under common control of an entity that is a minority shareholder of the Company and whose executive chairman

and founder served as a director of the Company through June 2022. The initial lease had a term of twelve months which automatically renews on an annual basis.

The rent expense under this operating lease was $0.15 million and $0.09 million for the years ended December 31, 2022 and 2021, respectively, which are included in loss from operations.

The Company made cash payments to ARE in connection with this operating lease in the amount of $0.14 million and $0.09 million during the years ended December 31, 2022 and 2021, respectively.

There were no amounts due to ARE under this operating lease at December 31, 2022 and 2021.

As of December 31, 2022, the Company's lease commitment is approximately $0.16 million.

13. Leases

The Company has commitments under operating leases for laboratory, warehouse, clinical trial sites and office space. The Company also has finance leases for manufacturing space and office equipment. The Company's leases have initial lease terms ranging from 3 years to 191 years. Certain lease agreements contain provisions for future rent increases. Payments due under the lease contracts include fixed payments.

Total rent expense recorded under these leases was $5.3 million and $5.0 million for the years ended December 31, 2022 and 2021, respectively.

As of December 31, 2022, the Company has short term lease commitments amounting to approximately $0.2 million on a monthly basis for one lease for vivarium space that is on a one-year lease.

On August 4, 2020, Meira Ireland entered into two agreements (the "Agreements") with Shannon Commercial Enterprises DAC trading as Shannon Commercial Properties, to acquire two properties in the Shannon Free Zone in Shannon, Ireland for an aggregate price of €18 million, or approximately $21.2 million. These properties will serve as the Company's second, large scale cGMP viral vector manufacturing facility and its first cGMP plasmid and DNA production facility.

The closing for the first building occurred in August 2020 and the closing for the second building occurred in January 2021. The total cost of the first and second buildings, including taxes and legal fees, was €11.9 million and €7.5 million, or approximately $13.8 million and $8.9 million, respectively, and have been recorded as right of use assets in the consolidated balance sheets as of December 31, 2021. There is no corresponding lease liability as the Company paid the full cost on the date of the closings.

At the closings, Meira Ireland entered into a lease for each property providing for a long leasehold interest of approximately 191 years.

The leases also include customary terms and conditions, with a nominal annual lease cost and annual maintenance fees of approximately €0.3 million, or approximately $0.4 million, in the aggregate, which amount is subject to change depending on the annual maintenance costs within the Shannon Free Zone development.

During the year ended December 31, 2022, the Company recognized three operating leases for locations in connection with its clinical trials for its IRD product candidates and office and warehouse space, with initial lease terms between 3 years and 9 years. Payments due under the lease contracts include fixed payments. In conjunction with these operating leases, the Company recognized initial operating lease right-of-use assets in the amount of $1.8 million and corresponding lease liabilities in the amount of $1.8 million which are included in the right-of-use assets and lease obligations in the consolidated balance sheets as of December 31, 2022.

During the year ended December 31, 2021, the Company recognized seven operating leases for locations in connection with its clinical trials for its IRD product candidates with initial lease terms between 5 years and 6 years. Certain lease agreements contain provisions for tenant allowances and future rent increases. Payments due under the lease contracts include fixed payments. In conjunction with these operating leases, the Company recognized initial operating lease right-of-use assets in the amount of $2.2 million and corresponding lease liabilities in the amount of $2.3 million which are included in the right-of-use assets and lease obligations in the consolidated balance sheets as of December 31, 2021.

The components of lease cost for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	2022	2021
Finance lease cost		
Amortization of right-of-use assets	$ 1,103	$ 1,227
Interest on lease liabilities	1	2
Total finance lease cost	1,104	1,229
Operating lease cost	5,307	5,002
Short-term lease cost	154	751
Total lease cost	$ 6,565	$ 6,982

Amounts reported in the consolidated balance sheets for leases where the Company is the lessee as of December 31, 2022 and 2021 were as follows (in thousands):

	December 31, 2022	December 31, 2021
Operating leases		
Right-of-use asset	$ 20,109	$ 22,782
Capitalized lease obligations	$ 21,215	$ 23,721
Finance leases		
Right-of-use asset	$ 24,718	$ 27,645
Capitalized lease obligations	$ —	$ 12
Weighted-average remaining lease term		
Operating leases	5.3 years	6.5 years
Finance leases	175.8 years	176.7 years
Weighted-average discount rate		
Operating leases	8.8 %	8.5 %
Finance leases	8.0 %	8.0 %

Other information related to leases as of the years ended December 31, 2022 and 2021 are as follows (in thousands):

	2022	2021
Cash paid for amounts included in the measurement of lease liabilities		
Operating cash flows from finance leases	$ 52	$ 16
Operating cash flows from operating leases	$ 5,384	$ 4,969
Financing cash flows from finance leases	$ —	$ 2
Right-of-use assets obtained in exchange for lease liabilities		
Operating leases	$ 1,793	$ 4,424
Finance leases	$ —	$ —

Future minimum lease payments under non-cancellable leases as of December 31, 2022 are as follows (in thousands):

	Operating Leases
2023	$ 5,513
2024	5,379
2025	5,338
2026	5,067
2027	1,794
Thereafter	2,872
Total undiscounted lease payments	$ 25,963
Less: Imputed interest	(4,748)
Total lease liabilities	$ 21,215

14. Debt Financing

On August 2, 2022 the Company, and the Subsidiary Guarantors, entered into the Financing Agreement with Perceptive. On December 19, 2022, the Financing Agreement was converted to a Note Purchase Agreement between the same parties and under substantially the same terms and conditions as the Financing Agreement, subject to certain customary note constitution terms.

The Note Purchase Agreement provides for an initial $75.0 million notes issuance (the "Tranche 1 Notes"), and the Company may request an additional $25.0 million notes issuance to be made available at Perceptive's sole discretion before August 2, 2024 (the "Tranche 2 Notes", together with the Tranche 1 Notes, the "Notes"). The Note Purchase Agreement matures on August 2, 2026 and is interest-only during the term. The Company has the option to redeem outstanding principal notes at any time along with an applicable early redemption fee. Outstanding amounts under the Note Purchase Agreement bear interest at a fluctuating rate per annum equal to 10.00% plus the secured overnight financing rate administered by the Federal Reserve Bank of New York for a one-month tenor, subject to a 1.00% floor. The annual interest rate was 13.02% at December 31, 2022. As of December 31, 2022, the outstanding balance of the Tranche 1 Notes was $75.0 million plus accrued interest of $4.0 million. During the year ended December 31, 2022, the Company recorded interest expense of $4.0 million.

The Company's obligations under the Note Purchase Agreement are secured by the Company's London, UK and Shannon, Ireland manufacturing facilities, $3.0 million of the Company's cash and the bank accounts of the Subsidiary Guarantors, and the issued and outstanding equity interests of the Subsidiary Guarantors.

The Note Purchase Agreement imposes covenants that include, among other things, enrolling in a Phase III trial for AAV-RPGR on or before June 30, 2023, and ensuring the Company's Shannon manufacturing facility meets or satisfies all applicable good manufacturing practice requirements on or before December 31, 2023, as well as various restrictions on the Company and the Subsidiary Guarantors, including restrictions pertaining to: (i) the incurrence of additional indebtedness, (ii) limitations on liens, (iii) limitations on certain investments, (iv) making distributions, dividends and other payments, (v) mergers, consolidations and acquisitions, (vi) dispositions of assets, (vii) the Company's maintenance of at least $3.0 million in a U.S. bank account, (viii) transactions with affiliates, (ix) changes to governing documents, (x) changes to certain agreements and leases and (xi) changes in control; however, certain of these restrictions contain exceptions which allow the Company to license, sell and monetize assets in its AAV-hAQP1 program in development to treat radiation-induced xerostomia, its AAV-GAD program in development to treat Parkinson's disease and its gene regulation platform technologies.

In connection with entering into the Financing Agreement, the Company granted warrants to Perceptive to purchase up to (i) 400,000 ordinary shares of the Company at an exercise price of $15.00 per share and (ii) 300,000 ordinary

shares of the Company at an exercise price of $20.00 per share. The warrants are exercisable immediately and expire on August 2, 2027. The Company recorded a debt discount of $2.3 million for the allocated fair value of the warrants.

The Company also capitalized certain lender and legal costs associated with the Note Purchase Agreement totaling $2.2 million, which were recorded as a discount to the loan. The aggregate discount of $4.4 million is being amortized to interest expense over the term of the Note Purchase Agreement. The Company amortized $0.4 million of the discount to interest expense during the year ended December 31, 2022. At December 31, 2022, the remaining unamortized discount was $4.0 million.

15. Commitments and Contingencies

There were no new material commitments or contingencies entered into during the year ended December 31, 2022.

16. Employee Benefit Plans

United States

On January 1, 2017, Meira LLC adopted a defined contribution retirement plan that complies with Section 401(k) of the Internal Revenue Code. All Meira LLC employees over the age of 21 are eligible to participate in the plan after three consecutive months of service. Employees are able to defer a portion of their pay into the plan on the first day of the month or after the day all age and service requirements have been met. The plan provides for a Company matching contribution. All eligible employees receive an employer matching contribution equal to the lesser of the amount the employee contributes to the plan or 6% of their salary up to the annual IRS limit.

United Kingdom

On August 1, 2016, Meira UK II adopted a defined contribution group personal pension plan that complies with HMRC for tax relief. All Meira UK II employees are eligible to participate in the plan upon joining the company and providing the required services. All eligible employees, if they elect to join the pension scheme, receive an employer pension contribution equal to 7.5% to 10.0% of their pensionable earnings. Currently, employees are required to contribute 0.5%, to meet minimum legal pension funding levels of 8%, but may make optional contributions up to the annual allowance HMRC limits.

Netherlands

Meira Netherlands operates a defined contribution pension. All of its employees participate in the plan. All eligible employees receive an employer pension contribution and are also required to contribute.

Ireland

On November 20, 2020, MeiraGTx Ireland adopted a defined contribution pension plan. All MeiraGTx Ireland employees are eligible to participate in the plan upon joining the Company. All eligible employees, if they elect to

join the pension scheme, receive an employer pension contribution. The Company's current contribution, exclusive of an employee match, is 4.5%, which exceeds Revenue Ireland requirements.

Belgium

Meira Belgium operates a defined contribution pension plan. All eligible employees receive an employer pension contribution of 8% of their annual salary. Employees do not make contributions to the plan.

During the years ended December 31, 2022 and 2021, employer contributions to all plans were $2.0 million and $1.8 million, respectively.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not Applicable.

ITEM 9A. CONTROLS AND PROCEDURES

Limitations on Effectiveness of Controls and Procedures

In designing and evaluating our disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer (principal executive officer) and Chief Financial Officer (principal financial officer), evaluated, as of the end of the period covered by this Form 10-K, the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")). Based on that evaluation, our Chief Executive Officer (principal executive officer) and Chief Financial Officer (principal financial officer) concluded that our disclosure controls and procedures were effective at the reasonable assurance level at the end of the period covered by this Form 10-K.

Management's Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Exchange Act Rule 13a-15(f). Our internal control over financial reporting is a process designed under the supervision of our Chief Executive Officer and Chief Financial Officer, and affected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. GAAP and includes policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets, (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of the effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies and procedures may deteriorate.

Management assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control—Integrated Framework (2013)*. Based on its assessment and those criteria, management has concluded that we maintained effective internal control over financial reporting as of December 31, 2022.

Exemption from Attestation Report of the Registered Public Accounting Firm on Internal Control Over Financial Reporting

This Form 10-K does not include an attestation report on our internal control over financial reporting from our independent registered public accounting firm since we qualify as an "emerging growth company" as defined under the JOBS Act.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

Not applicable.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item is incorporated by reference to our definitive proxy statement for our 2023 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2022.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item is incorporated by reference to our definitive proxy statement for our 2023 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2022.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

Securities Authorized for Issuance Under Equity Compensation Plans (as of December 31, 2022)

The following table provides information as of December 31, 2022, regarding our ordinary shares that may be issued under the MeiraGTx Holdings plc 2016 Equity Incentive Plan, as amended (the "2016 Plan"), the MeiraGTx Holdings plc 2018 Incentive Award Plan (the "2018 Plan") and the MeiraGTx Holdings plc 2018 Employee Stock Purchase Plan (the "2018 ESPP").

Plan category:	Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants, and Rights (a)	Weighted-Average Exercise Price of Outstanding Options, Warrants, and Rights (b)	Number of Securities Available for Future Issuance Under Equity Compensation Plans (excludes securities reflected in column(a)) (c)
Equity compensation plans approved by shareholders			
2016 Plan(1)	1,161,766	$ 5.27	—
2018 Plan (2) (3)	7,879,143	$ 15.82	843,802
2018 ESPP (4)	—	—	2,038,331
Equity compensation plans not approved by shareholders	—	—	—
Total	9,040,909	$ 14.03	2,882,133

(1) In connection with our IPO, we assumed the 2016 Plan. As the 2016 Plan was previously approved by our shareholders and, as we will not make future grants or awards under these plans, it is listed as "approved by shareholders." As such, the securities remaining available under the 2016 Plan have been excluded from the table above.

(2) Pursuant to the terms of the 2018 Plan, the number of ordinary shares available for issuance under the 2018 Plan automatically increases on each January 1, until and including January 1, 2028, by an amount equal to the lesser of: (a) 4% of the aggregate number of ordinary shares outstanding on the final day of the immediately preceding calendar year and (b) such smaller number of ordinary shares as is determined by our board of directors.

(3) The weighted average exercise price of outstanding awards does not take into account the shares issuable upon vesting of outstanding restricted share units which have no exercise price. At December 31, 2022 there were a total of 2,182,500 shares subject to restricted share units included in the Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants and Rights.

(4) Pursuant to the terms of the 2018 ESPP, the number of ordinary shares available for issuance under the 2018 ESPP automatically increases on each January 1, until and including January 1, 2028, by an amount equal to the lesser of: (a) 1% of the aggregate number of ordinary shares outstanding on the final day of the immediately preceding calendar year and (b) such smaller number of ordinary shares as is determined by our board of directors, subject to the limit set forth in the 2018 ESPP.

Other

The remaining information required by this Item is incorporated by reference to our definitive proxy statement for our 2023 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2022.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item is incorporated by reference to our definitive proxy statement for our 2023 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2022.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item is incorporated by reference to our definitive proxy statement for our 2023 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2022.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
3.1	Amended and Restated Memorandum and Articles of Association of the Registrant.	10-Q	001-38520	3.1	8/7/19	
4.1	Specimen Share Certificate evidencing the ordinary shares of the Registrant.	S-1	333-224914	4.1	5/29/18	
4.2	Shareholder Agreement.	10-K	001-38520	4.2	3/11/20	
4.3	Description of Securities.	10-K	001-38520	4.3	3/11/20	
4.4	Form of Warrant Agreement, dated August 2, 2022, issued by MeiraGTx Holdings plc to certain warrant holders.	10-Q	001-38520	4.1	11/10/22	
10.1#	2016 Equity Incentive Plan, as amended, and form of option agreements thereunder.	S-1/A	333-224914	10.1	5/29/18	
10.2#	2018 Incentive Award Plan and forms of award agreements thereunder.	S-1/A	333-224914	10.2	5/29/18	
10.3#	Non-Employee Director Compensation Program.	10-Q	001-38520	10.1	08/11/21	
10.4#	Form of Indemnification Agreement for Directors and Officers.	S-1/A	333-224914	10.4	5/29/18	
10.5	License and Sub-Lease Agreement, dated May 31, 2019, between MeiraGTx LLC and Imclone Systems, LLC.	10-Q	001-38520	10.2	8/7/19	
10.6	Lease Agreement, effective February 2, 2016, among MeiraGTx Limited, Moorfields Eye Hospital NHS, Foundation Trust and Kadmon Corporation LLC.	S-1	333-224914	10.6	5/14/18	
10.7#	Employment Agreement, dated February 15, 2016, between MeiraGTx Limited and Alexandria Forbes, Ph.D., as amended.	S-1/A	333-224914	10.7	5/29/18	
10.8#	Employment Agreement, dated February 15, 2016 between MeiraGTx Limited and Richard Giroux, as amended.	S-1/A	333-224914	10.8	5/29/18	
10.9#	Employment Agreement, dated April 27, 2015, between MeiraGTx Limited and Stuart Naylor, Ph.D., as amended.	S-1/A	333-224914	10.9	5/29/18	
10.10†	Agreement and Plan of Merger, dated December 31, 2015, among MeiraGTx Acquisition Corporation, BRI-Alzan, Inc., F-Prime Inc., Gregory Petsko, Dagmar Ringe, Brandeis University and MeiraGTx Limited.	S-1/A	333-224914	10.14	5/29/18	
10.11#	2018 Employee Share Purchase Plan.	S-1/A	333-224914	10.15	5/29/18	

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
10.12#	UK Sub-Plan Under the 2018 Incentive Award Plan.	10-K	001-38520	10.12	3/26/19	
10.13#	Form of Option Grant Notice and Option Agreement Under the UK Sub-Plan to the 2018 Incentive Award Plan.	10-K	001-38520	10.13	3/26/19	
10.14#	Form of Change in Control Agreement.	10-K	001-38520	10.14	3/11/21	
10.15	Lease agreement by and between Moorfields Eye Hospital NHS Foundation Trust and MeiraGTx UK II Limited, dated July 30, 2018.	10-Q	001-38520	10.4	8/8/18	
10.16	Lease agreement by and between Moorfields Eye Hospital NHS Foundation Trust and MeiraGTx UK II Limited, dated July 30, 2018.	10-Q	001-38520	10.5	8/8/18	
10.17	Transfer of Title, dated December 14, 2018, and Lease, dated October 12, 2001, relating to the Pharmacy Manufacturing Unit, Britannia Walk, London, England.	8-K	001-38520	10.1	12/14/18	
10.18	Overage Deed, dated December 14, 2018, between Moorfields Eye Hospital NHS Foundation Trust and MeiraGTx UK II Limited relating to the Pharmacy Manufacturing Unit, Britannia Walk, London, England.	8-K	001-38520	10.2	12/14/18	
10.19†	Consulting Agreement, dated October 5, 2018, between MeiraGTx Holdings plc, Vector Consulting LLC, Michael G. Kaplitt, Matthew During, and Stephen B. Kaplitt.	10-K	001-38520	10.19	3/26/19	
10. 20†	License Agreement (RPE65), dated January 29, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx UK II Limited and MeiraGTx Limited.	10-K	001-38520	10.20	3/26/19	
10. 21†	License Agreement (CNGB3), dated January 29, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx Holdings plc, MeiraGTx UK II Limited and MeiraGTx Limited.	10-K	001-38520	10.21	3/26/19	
10. 22†	License Agreement (CNGA3), dated January 29, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx UK II Limited and MeiraGTx Limited.	10-K	001-38520	10.22	3/26/19	

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
10. 23†	License Agreement (RPGR), dated February 5, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx UK II Limited and MeiraGTx Limited.	10-K	001-38520	10.23	3/26/19	
10. 24†	Amendment No. 4 to Exclusive License Agreement, dated January 29, 2019, between UCLB and MeiraGTx Limited.	10-K	001-38520	10.24	3/26/19	
10. 25†	Collaboration, Option and License Agreement, dated January 30, 2019, by and among Janssen Pharmaceuticals, Inc., MeiraGTx UK II Limited and MeiraGTx Holdings plc.	10-K	001-38520	10.25	3/26/19	
10.26††	First Amendment to Collaboration, Option and License Agreement, dated December 16, 2021.	10-K	001-3852	10.26	3/10/22	
10. 27	Registration Rights Agreement, dated February 26, 2019, by and among MeiraGTx Holdings plc and the investors named therein.	8-K	001-38520	10.2	2/26/19	
10.28	Agreement for Lease with Landlord's Refurbishment Works, dated May 29, 2019, between MeiraGTx UK II Limited and Provost 1 Limited and Provost 2 Limited, including agreed form of Lease between MeiraGTx UK II Limited and Provost 1 Limited and Provost 2 Limited.	10-Q	001-38520	10.3	8/7/19	
10.29#	Form of Restricted Share Unit Grant Notice and Restricted Share Unit Agreement Under the 2018 Incentive Award Plan.	10-K	001-38520	10.30	3/11/20	
10.30#	Form of Restricted Share Unit Grant Notice and Restricted Share Unit Agreement Under the UK Sub-Plan to the 2018 Incentive Award Plan.	10-K	001-38520	10.31	3/11/20	
10.31	Particulars and Conditions of Sale of Building 2, Block K, Shannon Free Zone, Shannon, County Clare, Ireland, dated as of August 4, 2020, by and between Shannon Commercial Enterprises DAC trading as Shannon Commercial Properties and MeiraGTx Ireland DAC, including agreed form of Lease between Shannon Commercial Enterprises DAC and MeiraGTx Ireland DAC.	10-Q	001-38520	10.1	11/5/20	
10.32	Particulars and Conditions of Sale of Building 3, Block K, Shannon Free Zone, Shannon, County Clare, Ireland, dated as of August 4, 2020, by and between Shannon Commercial Enterprises DAC trading as Shannon Commercial Properties and MeiraGTx Ireland DAC, including agreed form of Lease between Shannon Commercial Enterprises DAC and MeiraGTx Ireland DAC.	10-Q	001-38520	10.2	11/5/20	
10.33#	Deferred Compensation Plan for Non-Employee Directors.	10-K	001-38520	10.35	3/10/22	

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
10.34#	Form of Restricted Share Unit Grant Notice and Restricted Share Unit Agreement for Non-Employee Directors Under the 2018 Incentive Award Plan.	10-K	001-38520	10.36	3/10/22	
10.35††	Credit Agreement and Guaranty, dated August 2, 2022, by and among MeiraGTx Holdings plc, as borrower, MeiraGTx UK II Limited and MeiraGTx Ireland DAC, as guarantors, the lenders and other parties from time to time party thereto and Perceptive Credit Holdings III, LP, as administrative agent and lender.	10-Q	001-38520	10.1	11/10/22	
10.36	Amendment No. 1 to Credit Agreement and Guaranty, dated December 19, 2022, by and among MeiraGTx Holdings plc, as borrower, certain subsidiary guarantors and lenders party thereto, and Perceptive Credit Holdings III, LP, as administrative agent.					*
10.37††	Amended and Restated Note Purchase Agreement and Guaranty, dated December 19, 2022, by and among MeiraGTx Holdings plc, as issuer, the subsidiary guarantors and noteholders from time to time party thereto, and Perceptive Credit Holdings III, LP, as administrative agent.					*
10.38	Tranche 1 Note, dated December 19, 2022, by and among MeiraGTx Holdings plc, as issuer, the subsidiaries guarantors and noteholders from time to time party thereto, and Perceptive Credit Holdings III, LP, as administrative agent.					*
10.39	Securities Purchase Agreement, dated November 9, 2022, by and among MeiraGTx Holdings plc and Johnson & Johnson Innovation – JJDC, Inc.					*
10.40	Registration Rights Agreement, dated November 15, 2022, by and among MeiraGTx Holdings plc and Johnson & Johnson Innovation – JJDC, Inc.					*
21	List of Subsidiaries.					*
23.1	Consent of Ernst & Young LLP.					*
31.1	Certification of Chief Executive Officer pursuant to Rules 13a-14(a)/15d-14(a) under the Securities Exchange Act of 1934, as amended.					*
31.2	Certification of Chief Financial Officer pursuant to Rules 13a-14(a)/15d-14(a) under the Securities Exchange Act of 1934, as amended.					*
32.1	Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					**

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
32.2	Certification of Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					**
101.INS	Inline XBRL Instance Document.					*
101.SCH	Inline XBRL Taxonomy Extension Schema Document.					*
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.					*
101.DEF	Inline XBRL Taxonomy Definition Linkbase Document.					*
101.LAB	Inline XBRL Taxonomy Label Linkbase Document.					*
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.					*
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).					*

* Filed herewith
** Furnished herewith
# Management contract or compensation plan or arrangement
† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment pursuant to Rule 406 under the Securities Act of 1933, as amended
†† Portions of this exhibit (indicated by asterisks) have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K

Certain agreements filed as exhibits to this Form 10-K contain representations and warranties that the parties thereto made to each other. These representations and warranties have been made solely for the benefit of the other parties to such agreements and may have been qualified by certain information that has been disclosed to the other parties to such agreements and that may not be reflected in such agreements. In addition, these representations and warranties may be intended as a way of allocating risks among parties if the statements contained therein prove to be incorrect, rather than as actual statements of fact. Accordingly, there can be no reliance on any such representations and warranties as characterizations of the actual state of facts. Moreover, information concerning the subject matter of any such representations and warranties may have changed since the date of such agreements.

ITEM 16. FORM 10-K SUMMARY

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) 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.

MeiraGTx Holdings plc (Registrant)

Date: March 14, 2023

By: /s/ Alexandria Forbes
Alexandria Forbes
President and Chief Executive Officer and
Director (Principal Executive Officer)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Alexandria Forbes, Ph.D. Alexandria Forbes, Ph.D.	President and Chief Executive Officer and Director (Principal Executive Officer)	March 14, 2023
/s/ Richard Giroux Richard Giroux	Chief Financial Officer (Principal Financial and Accounting Officer)	March 14, 2023
/s/ Keith R. Harris, Ph.D. Keith R. Harris, Ph.D.	Chairman of the Board and Director	March 14, 2023
/s/ Ellen Hukkelhoven, Ph.D. Ellen Hukkelhoven, Ph.D.	Director	March 14, 2023
/s/ Martin Indyk, Ph.D. Martin Indyk, Ph.D.	Director	March 14, 2023
/s/ Arnold J. Levine, Ph.D. Arnold J. Levine, Ph.D.	Director	March 14, 2023
/s/ Lord Mendoza Lord Mendoza	Director	March 14, 2023
/s/ Nicole Seligman Nicole Seligman	Director	March 14, 2023
/s/ Thomas E. Shenk, Ph.D. Thomas E. Shenk, Ph.D.	Director	March 14, 2023
/s/ Debra Yu, M.D. Debra Yu, M.D.	Director	March 14, 2023