MeiraGTx Holdings plc

Nasdaq: MGTX

MEIRAGTX.COM

2018 ANNUAL REPORT

MEIRAGTX HOLDINGS PLC

MEIRAGTx

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, 2018

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	**Not applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
430 East 29th Street, 10th Floor New York, NY	**10016**
(Address of principal executive offices)	**(Zip Code)**

(646) 490 2965
(Registrant's telephone number, including area code)

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

Title of each class	**Name of exchange on which registered**
Ordinary Shares, $0.00003881 Nominal value	**Nasdaq**

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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

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

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

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

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

As of June 30, 2018, the aggregate market value of the registrant's ordinary shares held by non-affiliates of the registrant was approximately $154.6 million (based upon the closing sale price of the registrant's ordinary shares on that date on the Nasdaq Global Select Market).

As of March 15, 2019, the registrant had 33,183,734 ordinary shares outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement relating to its 2019 annual shareholder meeting to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018 are incorporated herein by reference in Part III.

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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, 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.

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.

BASIS OF PRESENTATION

On June 7, 2018, in connection with its initial public offering (the "IPO"), MeiraGTx Holdings plc, an exempted company incorporated under the laws of the Cayman Islands, acquired all the issued and outstanding ordinary shares of MeiraGTx Limited pursuant to a series of reorganization transactions. We refer to these events in this Form 10-K as the "Reorganization Transactions." Prior to the Reorganization Transactions, MeiraGTx Holdings plc had not conducted any operations and had nominal assets and liabilities.

Unless the context otherwise requires, references in this Form 10-K to "Meira," "we," "us", "our" or "the Company" refer to (i) MeiraGTx Limited and its subsidiaries prior to the Reorganization Transactions and (ii) MeiraGTx Holdings plc and its subsidiaries upon completion of the Reorganization Transactions, as applicable.

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 five 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 technology. 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. Though initially focusing on the eye, salivary gland and central nervous system, 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 that we expect can supply our current 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 UK Medicines and Healthcare products Regulatory Agency. On December 14, 2018, we acquired from Moorfields Eye Hospital NHS Foundation Trust of Moorfields Eye Hospital a long leasehold interest, (the "Head Lease"), in the site of our manufacturing facility, 92 Britannia Walk, London N1 7LU, for a purchase price of £5,250,000 (approximately $6,615,000 assuming a rate of $1.26 per GBP on the date of the acquisition. As a result of this transaction, we are now the tenant under the Head Lease, which has a remaining term of 108 years, with no facility rent due

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.

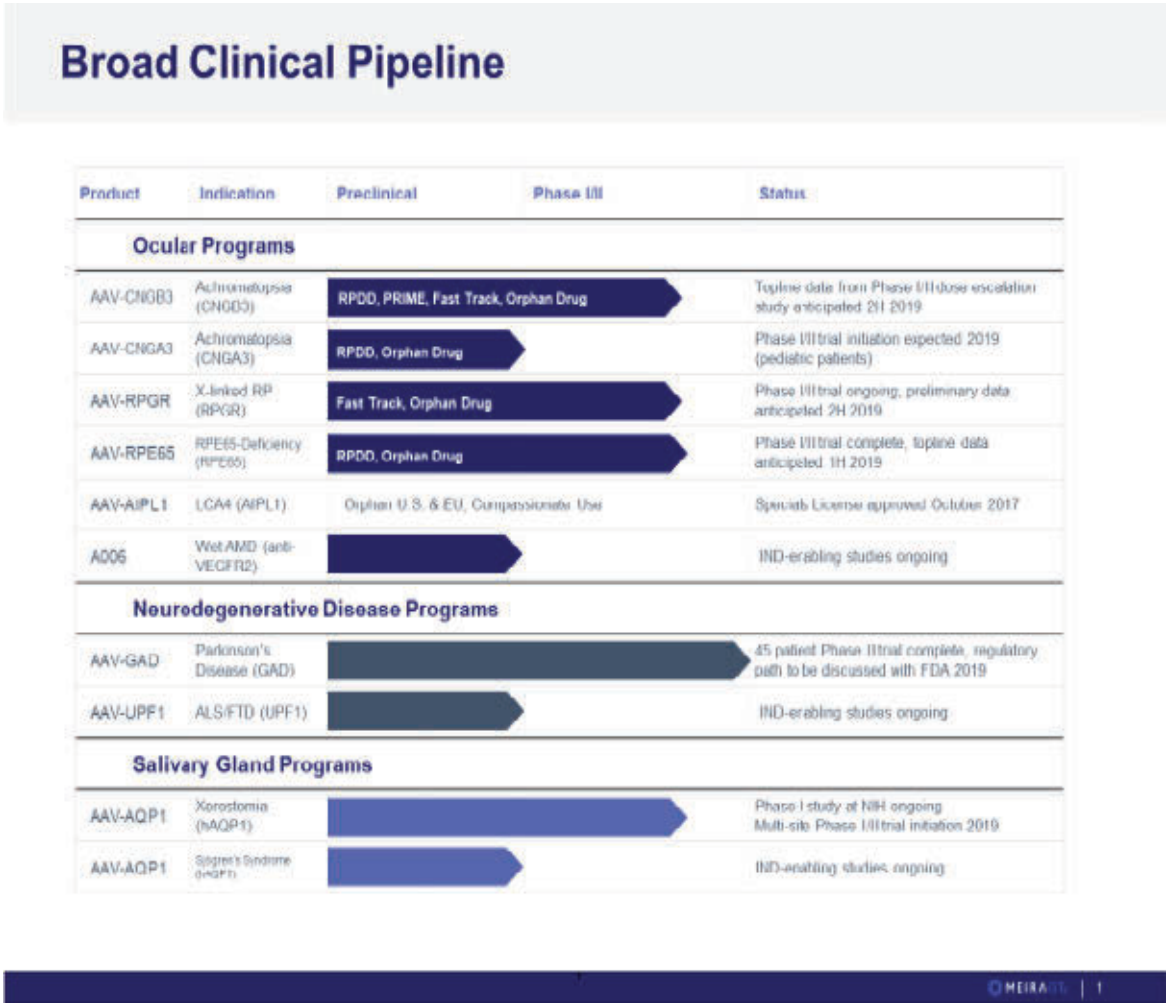
We are also developing a potentially transformative technology to enable the use of small molecules to turn gene therapy product candidates on and off. The aim of this gene regulation platform is to convert gene therapy into a generalizable delivery mechanism for biologic drugs using a small molecule "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: inherited retinal diseases, or IRDs, 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 15, 2019 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 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 that was executed on January 30, 2019.



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:

- neovascular age related macular degeneration, or wet AMD – use of 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;
- 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;
- amyotrophic lateral sclerosis, or ALS—targeting dysregulation of neuronal RNA, processing, which we believe may lead to the degeneration of motor neurons that occurs in ALS;
- Alzheimer's disease—targeting endosomal trafficking, which is a central mechanism that we believe underlies Alzheimer's disease; and
- gene regulation—use of our proprietary RNA shape regulation cassette to switch gene therapy product candidates on and off with small molecules, potentially transforming gene therapy technology into a delivery mechanism for a broad array of biologic drugs.

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 currently have three ongoing Phase 1/2 clinical programs in IRDs, with an additional program expected to initiate a Phase 1/2 clinical trial in 2019. The targets of our three ongoing Phase 1/2 ophthalmology programs include achromatopsia, or ACHM, related to mutations in *CNGB3*, X-linked retinitis pigmentosa related to mutations in *RPGR*, or XLRP-RPGR, and inherited retinal dystrophy caused by mutations in *RPE65*, or *RPE65*-deficiency. We also have a product candidate that was manufactured and released for compassionate use under a specials license in the United Kingdom to treat patients with Leber congenital amaurosis 4, or LCA4, caused by mutations in *AIPL1*. For each of our Phase 1/2 clinical programs we have a prospectively designed natural history study ongoing, which includes the same endpoints as our corresponding gene therapy treatment trial. We believe use of these natural history studies differentiates our programs by providing patient populations to facilitate the efficient execution of our clinical trials and offering insight into the appropriate endpoints for regulatory approval of our gene therapy product candidates. In addition to these clinical programs in IRDs, we have preclinical programs that apply novel approaches to both wet and dry AMD.

The FDA and EMA have granted orphan drug designation to each product candidate in our ongoing clinical programs, including those treating mutations in *CNGB3*, *RPGR* and *RPE65*, as well our product candidates for the treatment of achromatopsia due to autosomal-recessive *CNGA3* gene mutations and to treat mutations in *AIPL1*. The FDA has also granted rare pediatric disease designation for our clinical programs treating mutations in *RPE65* and *CNGB3* and our product candidate for the treatment of autosomal-recessive *CNGA3* gene mutations, and Fast Track designation to our clinical programs for the treatment of achromatopsia caused by *CNGB3* gene mutations to improve visual function and for the treatment of XLRP caused by mutations in *RPGR*. We have also received PRIME designation from the EMA for our clinical program treating mutations in *CNGB3*.

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.

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. A Phase 1 clinical trial of our gene therapy product candidate, AAV-AQP1, is ongoing in patients who have survived cancer free for five or more years following treatment for head and neck cancer and are suffering from grade 2 or 3 radiation induced late xerostomia, or RIX. There are approximately 170,000 grade 2 or 3 RIX patients who have survived two or more years after radiation treatment for head and neck cancer in the United States, with approximately 10,000 new cases each year. We also intend to initiate a Phase 1/2 clinical trial of AAV-AQP1 for the treatment of patients with chronic xerostomia caused by Sjogren's syndrome, an autoimmune disease affecting more than two million people in the United States.

The FDA has granted orphan drug designation to AAV-AQP1.

Our Neurodegenerative Disease Programs

Neurodegenerative diseases are our third area of focus. Our first target indication is Parkinson's disease, where we have Phase 2 clinical data from a successful randomized, double-blind, sham-controlled trial. 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 result in normalization 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. To date, we have not had any formal meetings with regulatory agencies nor determined the regulatory pathway and any potential related development costs for our recently acquired AAV-GAD gene therapy program for Parkinson's disease.

Our second target indication is ALS, where we currently have IND-enabling studies ongoing. We believe our approach to treating ALS patients is differentiated because, rather than targeting a specific genetic defect that defines a small subset of ALS patients, we aim to target the underlying cell biology driving motor neuron death in ALS, potentially enabling us to treat a broader patient population that includes both sporadic and inherited forms of the disease. Increasing evidence suggests a critical role of RNA metabolism in neuronal cells, in particular in motor neurons that are specifically affected in ALS. We believe that dysregulation of neuronal RNA processes results in the degeneration of motor neurons that leads to ALS. Using our viral vector product candidate, AAV-UPF1, we target the central quality control system regulating RNA in motor neurons with the aim of enhancing motor neuron survival in ALS patients.

We have an Alzheimer's disease program that is likewise directed towards the underlying cell biology of the disease, in this case endosomal trafficking, a mechanism cells use to cycle proteins to the cell surface. Over the past decade, evidence has emerged supporting endosomal trafficking dysfunction in neurons as a central process in the early etiology of Alzheimer's disease. In particular, a master regulator of trafficking out of the endosomes, called retromer, has been implicated. We are in the process of identifying what we believe to be the optimal approach to restoring normal endosomal function to the neurons that are the first to be affected in Alzheimer's. In parallel, we are developing and validating biomarkers of endosomal dysfunction and pre-symptomatic Alzheimer's disease. We believe this approach may also provide a framework for treating certain forms of Parkinson's disease that are also associated with endosomal dysfunction.

Our Strengths

In addition to our four ongoing clinical programs, we have a broad pipeline of preclinical programs, core capabilities in viral vector design and optimization, gene therapy manufacturing and a potentially transformative gene regulation technology. 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 Technology Platform:** 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, which we expect can supply all of our current clinical and preclinical programs through regulatory approval and, should they be approved, provide sufficient capacity for their commercial production.

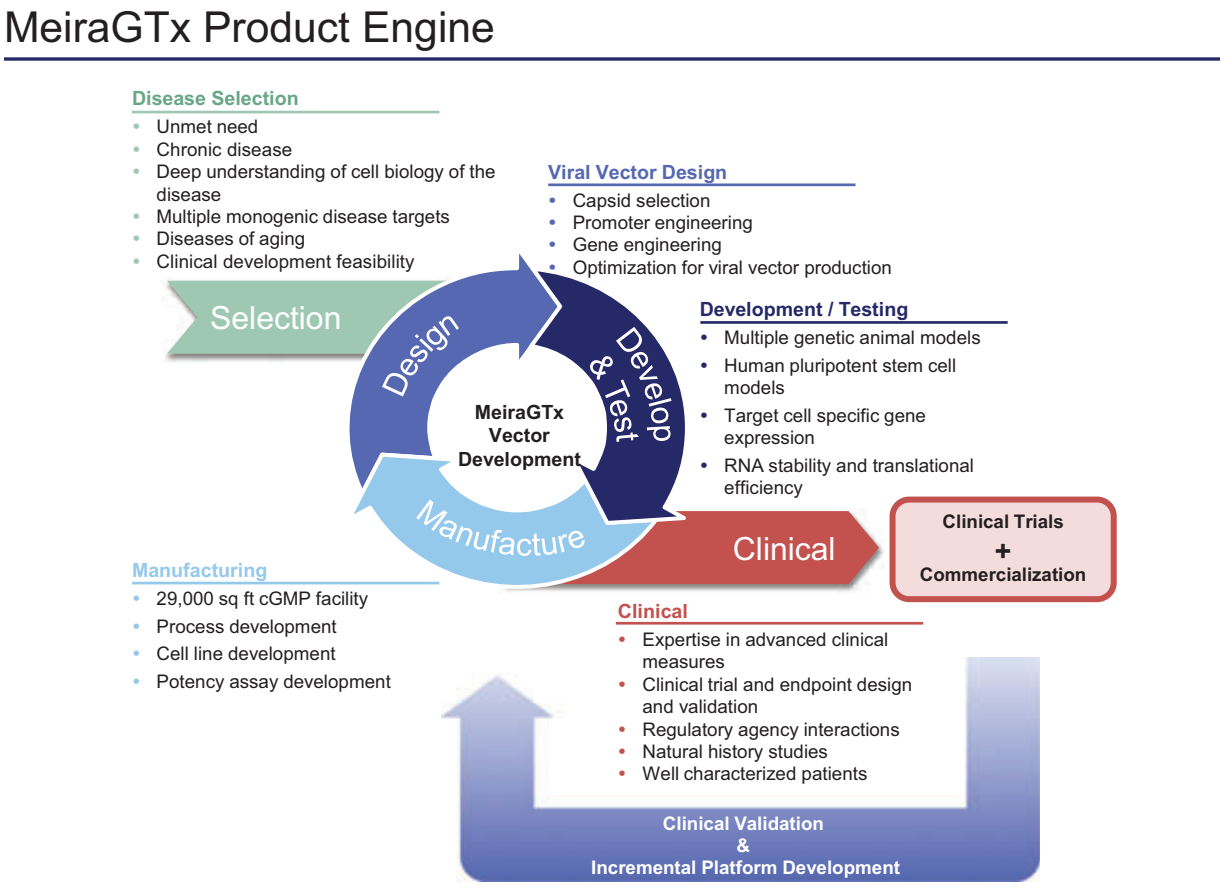
- **Robust and Diverse Clinical and Preclinical Pipeline:** Applying our portfolio approach to gene therapy product development, our initial focus is on treatments for IRDs, salivary glands disorders and neurodegenerative diseases with potential for accelerated approval and has produced five programs in clinical development and multiple preclinical development programs.
- **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 to treat disorders of the eye and salivary gland;
- continue to advance the development of our pipeline of product candidates for the treatment of neurodegenerative disorders;
- utilize our viral vector design and optimization capabilities to identify and develop new gene therapies for other 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 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.

The figure below depicts the steps in our product engine, including disease selection, design, development/testing, clinical and manufacturing:



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, more than 2,300 gene therapy studies covering a broad range of disease targets have been initiated. Recently, the first gene therapies have received regulatory approval, including approval by the FDA of Luxturna for an ophthalmology condition, resulting in a growing acceptance of gene therapy technology as a potentially safe and effective therapeutic approach.

Our current programs use the 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 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 clinical IRD programs.

Rather than 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. 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 Ophthalmology Programs

Overview and Strategy

We currently have three ongoing Phase 1/2 clinical programs targeting IRDs, including ACHM related to mutations in *CNGB3*, XLRP-RPGR and *RPE65*-deficiency, with an additional program expected to enter a Phase 1/2 clinical trial in 2019 in patients with ACHM related to mutations in *CNGA3.* We also have a product candidate that was manufactured and released for compassionate use under a specials license in the UK to treat LCA4 patients. 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 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.

Two of our clinical-stage product candidates are targeting IRD indications in achromatopsia caused by mutations in the *CNGB3* gene and inherited retinal dystrophy caused by mutations in the *RPE65* gene. The primary defect in these particular genetic disorders is the absence of function of one of the two different types of photoreceptors that constitute the light sensing part of the retina, rods or cones. In achromatopsia, the cones completely lack function, while in *RPE65*-deficiency it is the rods that lack function. In these indications, we anticipate that restoring a normal copy of the mutant gene to the retina of patients with these genetic disorders may restore function to the particular type of photoreceptor that is defective in each of these indications. Although cone photoreceptors are generally preserved during childhood in *RPE65*-deficient patients, the lack of healthy active rods eventually affects the cones that they support and over time both rods and cones die, the retina degenerates and *RPE65*-deficient patients become totally blind.

We also have a clinical-stage product candidate for XLRP-RPGR, in which all photoreceptors, both rods and cones, function poorly, leading to degeneration of the retina and total blindness. We have used data and learnings from our *RPE65* studies to inform the design and techniques used in our XLRP-RPGR program. The aim of our XLRP-RPGR treatment is to slow the degeneration of the retina, which we measure using validated surrogate structural endpoints and changes in the detailed structural maps of these patients' retinas over time.

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. We have a preclinical program using an anti-VEGFR2 antibody targeting wet AMD and we are currently conducting IND-enabling studites for this program. We are also working to integrate our gene regulation technology with our wet AMD program. Our ultimate aim is to activate the anti-VEGFR2 antibody gene that we have installed in the eye with a small molecule applied topically in an eye drop. This could potentially allow for intermittent dosing of the antibody using an eye drop rather than injection. 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.

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, as well as commercial synergies, if these product candidates are approved by the FDA and other regulatory authorities.

Our Competitive Advantage: Natural History Studies, Relationships with Leading Institutions and Our cGMP Manufacturing Facility

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 United States and European Union affected by IRDs. However, IRDs may be caused by mutations in over 200 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 1/2 trials.

The lead investigator for the natural history studies is Michel Michaelides, Professor of Ophthalmology at Moorfields Eye Hospital in London. For each of the natural history studies, baseline assessments are made upon enrollment, with follow up assessments at six-month intervals for two years and annual assessments for up to an additional three years. 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 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. Our relationships with these institutions, in most cases, precede the date on which we entered into a clinical site agreement with the applicable institution. Professor Robin Ali, Ph.D., our Head of Preclinical Ophthalmology and one of our founders, is Professor of Human Molecular Genetics at UCL Institute of Ophthalmology and Theme Leader for Gene Therapy at NIHR Biomedical Research Centre for Opthalmology, Moorfields Eye Hospital in London, and a Visiting Professor at the University of Michigan Kellogg Eye Center. These institutions 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. These institutions provide services with respect to our preclinical and clinical studies. For example, all of our IRD clinical trials are being conducted at Moorfields Eye Hospital in London, University of Michigan Kellogg Eye Center and Massachusetts Eye and Ear Hospital in Boston. 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. Achromatopsia

Disease Background and Market Opportunity

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.

Cones and rods are the two kinds of photoreceptors in the human eye. Photoreceptors are light-sensitive cells that absorb light and convert it into an electrical signal that is transmitted to the brain for the perception of light, or vision. Rods can detect very low levels of light and are quickly inactivated in higher light levels, enabling vision in dim light. Cones, on the other hand, remain active in high light levels and support daytime vision and the perception of color. Even though only 5% of the photoreceptors in the eye are cones, they are concentrated in the central part of the retina, the macula, where they are tightly packed, thus enabling high-acuity daytime vision. The highest cone density is in the centermost spot of the macula, called the fovea. Since cones are essential for central visual acuity, color vision, and most daily visual activities, 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. To date, mutations of any one of six genes encoding components of the light sensing machinery of cone photoreceptors have been

identified as causing ACHM. The *CNGB3* and *CNGA3* genes are the two most common of these genes, together accounting for up to 92% of ACHM cases, with *CNGB3* slightly more common than *CNGA3* in most geographic territories. Together, the proteins encoded by the *CNGB3* and *CNGA3* genes make up the cone-specific cyclic nucleotide gated, or CNG, channel, which is essential for cones to produce an electrical signal in response to light. Mutations in either of these genes prevent the formation of the CNG channel.

There are estimated to be approximately 12,000 patients with ACHM caused by mutations in *CNGB3* in the United States, Japan and Germany, France, Spain, Italy and the United Kingdom, or 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.

Our Gene Therapy Program

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.

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.

ACHM Caused by Mutations in CNGB3

With our collaborators at the University College of London's Institute of Ophthalmology, or UCL IO, led by Professor Robin Ali, we have developed a product candidate 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 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.

Preclinical studies in mice lacking the *Cngb3* gene were carried out by our collaborators at UCL IO and led by Professor Robin Ali in 2010 and 2011 and the data was published in *Human Molecular Genetics* in 2011. In these studies, it was observed that delivery of our *CNGB3* product candidate, AAV-CNGB3, via subretinal injection at doses between $6E^9$ and $8E^9$ viral genomes per eye, or vg/eye, was associated with a restoration of cone function to near normal levels.

In one of these studies, retinal response to light was measured in three groups of mice: *Cngb3* mutant mice treated with AAV-CNGB3, untreated *Cngb3* mutant mice and normal mice. Mice were treated with AAV-CNGB3 vector dosed at $2E^{12}$ vg/mL ($8E^9$ vg/eye) via subretinal injection. One eye was treated per mouse. Vector was administered when mice were 30 days old, and electrical responses, or ERGs, of the retina were measured 90 days following administration of the vector.

Figure 1 shows representative ERG responses of the retina to different light stimuli: a single flash of bright light (1A; 1B; 1C) and repeated pulses, or flickers, of bright light at different frequencies to assess the refresh rate of the photoreceptors (1A'; 1B'; 1C'). Retinas from three different groups of mice were tested: retinas of normal mice (Figure 1A), retinas of mutant mice lacking the *Cngb3* gene (Figure 1B) and retinas of mutant mice lacking the *Cngb3* gene, but treated with AAV-CNGB3 (Figure 1C). It was observed that the response to a bright light pulse was largely absent in the retinas of *Cngb3* mutant mice, as this response is largely mediated by the cones and is therefore severely impacted by the *Cngb3* mutation (Figure 1B). It was also observed that treatment of *Cngb3* mutant mice with AAV-CNGB3 was associated with a high-degree of restored cone function in these mutant mouse retinas in response to a single flash of bright light (Figure 1C). In addition, we tested the response of cones to rapid flickers of bright light (Figure $1A^1$) because only cones can register multiple sequential signals from rapid flickers. It was observed that registering rapid flickers was also impacted by the *Cngb3* mutation (Figure $1B^1$) and the cone flicker response was nearly completely restored in the retinas of *Cngb3* mutant mice following treatment with AAV-CNGB3 (Figure $1C^1$).

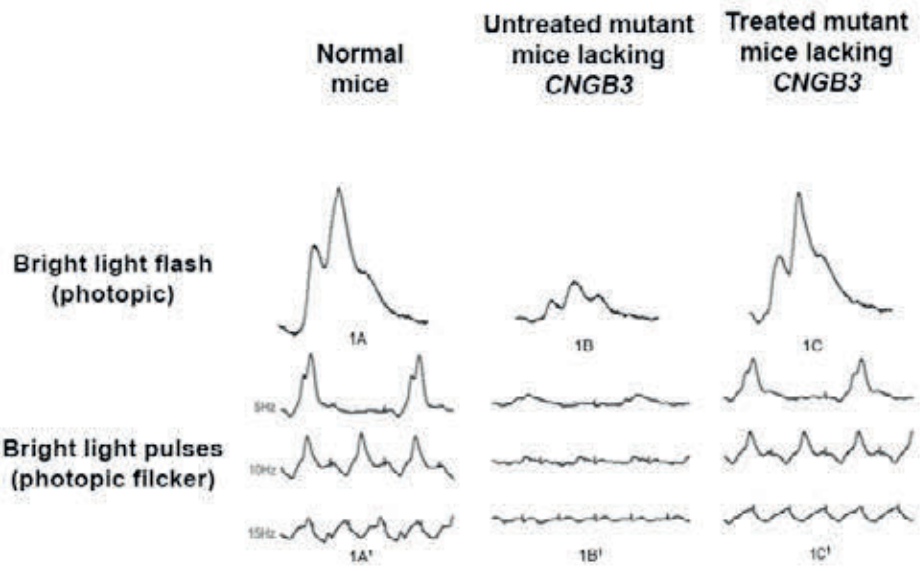


Figure 1. Electrical responses of the retina reacting to two different light stimuli: a single flash of bright light and repeat pulses of bright light at increasing frequency, or flickers.

Figure 1A and $1A^1$. The electrical responses of the retina from a normal mouse reacting to a flash of bright light and flickers.

Figure 1B and $1B^1$. The electrical responses of the retina from a mutant mouse lacking *Cngb3* reacting to a flash of bright light and flickers.

Figure 1C and 1C[1]. The electrical responses of the retina from a mutant mouse lacking *Cngb3* treated with AAV-CNGB3 reacting to a flash of bright light and flickers. Treatment with AAV-CNGB3 was associated with a high degree of restoration of cone function, with the electrical response to a bright flash of light and rapid flickers nearly matching the response observed in the normal mouse retina.

In another one of the preclinical studies carried out by our collaborators at UCL IO, it was assessed whether functional improvement at the retinal level of *Cngb3* mutant mice was impacted by the age of the mice at the time treatment with the gene therapy product candidate. In this study, *Cngb3*-mutant mice were treated with AAV-CNGB3 at 30 days old, the P30 group, or 180 days old, the P180 group. One eye was treated in each mouse via subretinal injection dosed at $2E^{12}$ vg/mL ($8E^{9}$ vg/eye). Optomotor measurements were taken 60 days after treatment of the P30 group of the *Cngb3* mutant mice treated with AAV-CNGB3 (n=11), untreated *Cngb3* mutant mice (n=11) and normal, age-matched untreated mice (n=5). Optomotor measurements were also taken 60 days after the treatment of the P180 group of the *Cngb3* mutant mice treated with AAV-CNGB3 (n=6), untreated *Cngb3* mutant mice (n=6) and normal, age-matched untreated mice (n=5). Optomoter assessments were made by placing each mouse on a pedestal located in the center of four inward facing computer screens, that projected a rotating image. The head-tracking responses of each mouse was observed using an overhead infrared video camera. Visual acuity was measured by involuntary reflex head-tracking responses driven by the left (clockwise rotations, black arrow) and right (counter-clockwise rotations, white arrow) eyes, respectively (Figure 2A).

Figure 2B is a graph comparing the visual acuity as measured by the average optomotor assessment of the normal eyes, eyes from *Cngb3* mutant mice treated with AAV-CNGB3 and eyes from *Cngb3*-mutant mice that were untreated. It was observed that *Cngb3* mutant mice had a significantly lower visual acuity than normal mice. However, after treatment with AAV-CNGB3, visual acuity in the *Cngb3* mutant mice eyes treated at 30 days old was observed to be restored to a similar level as that observed in normal mice. In contrast, no significant difference in visual acuity between the treated and untreated eyes was observed when treatment was given at 180 days old. Data from this study suggests that treatment received at an older age is less capable of restoring visual acuity.

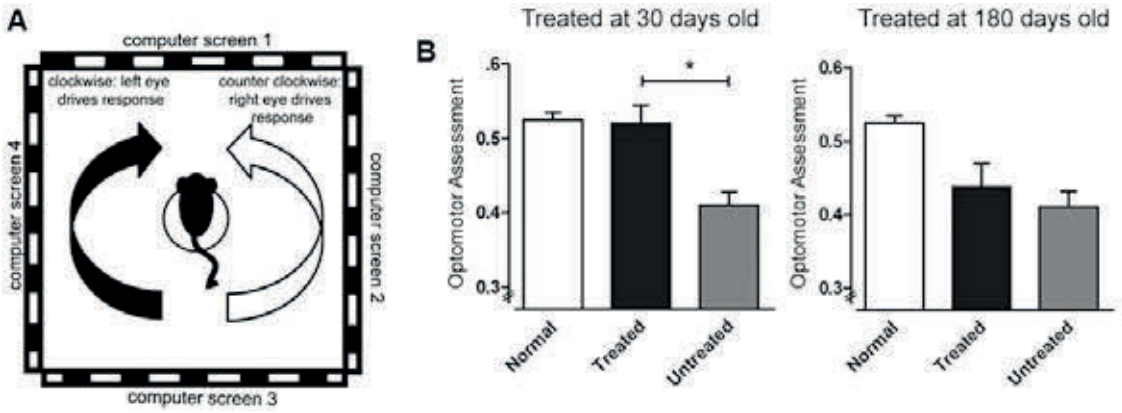


Figure 2A. Depiction of how optomotor assessments were taken. Each mouse was placed on a pedestal located in the center of four inward facing screens and was observed by an overhead infrared video camera. The assessments were made 60 days following treatment of the *Cngb3* mutant mice with AAV-CNGB3 at 30 days old and 180 days old.

Figure 2B. Graph showing averaged optomotor assessment of each group. Visual acuity, as measured by the optomotor assessment, was observed to be restored to normal levels in the mouse treated at 30 days old (left panel) but not in the mouse treated at 180 days old (right panel).

Between October 2016 and December 2016, we carried out a dose-ranging preclinical study at UCL IO to determine the efficacy of different doses of AAV-CNGB3 in rescuing cone response to a single pulse of bright

light in *Cngb3* mutant mice as measured by electrical responses across the retina, or ERG. The study was conducted to support a planned Phase 1/2 clinical trial in patients with *CNGB3* mutations following the FDA's request for additional rescue data at a range of different doses. While long-term functional rescue was observed in prior tests, there was no dosage titration tested in those studies. The data from this study has not been published.

We assessed cone-mediated ERG responses in *Cngb3* mutant mice at three doses and compared these responses to baseline recordings of untreated eyes at two different time-points following treatment. *Cngb3* mutant mice were administered AAV-CNGB3 via subretinal injection of 4uL of vector at each dose. Mice were treated at four weeks of age and ERG responses were measured in these mice at four weeks and eight weeks following treatment. Three eyes were treated at each of the three doses, and three eyes were untreated. The reviewer analyzing the ERG traces was masked to which eye received treatment.

Figure 3 shows the photopic ERG amplitudes measured to assess cone photoreceptor function in *Cngb3* mutant mice treated with AAV-CNGB3 at $1E^{11}$ vg/mL ($4E^{8}$ vg/eye; n=3), $3E^{11}$ vg/mL ($1.2E^{9}$ vg/eye; n=3) and $1E^{12}$ vg/mL ($4E^{9}$ vg/eye; n=3), and untreated eyes (n=3) at four and eight weeks post administration. A photopic ERG is the electrical response of the retina corresponding to cone electrical activity following a single pulse of bright light (single ERG recordings are shown in Figure 1). The higher the ERG amplitude, the greater the response of the retina to bright light. These data show a statistically significant increase in cone ERG responses for all three doses of AAV-CNGB3 and for both time-points following vector administration except for low dose at four weeks post injection (p=0.051). These data indicate that AAV-CNGB3 is associated with the rescue of the cone electrical response in the retina of *Cngb3* mutant mice in a dose-responsive fashion. While initial responses were observed in mice four weeks after subretinal injection of the vector, at all three doses significantly stronger ERG responses were observed eight weeks after vector administration, with the maximum ERG response observed at the highest dose eight weeks after administration.

In this study, a dose response in ERG amplitudes from treated eyes was observed, suggesting that increasing amounts of AAV-CNGB3 is associated with greater rescue of responses in *Cngb3* mutant mice. The three doses tested in this study are the same as those doses administered in our AAV-CNGB3 Phase 1/2 clinical trial on a vg/mL of viral vector titer basis.

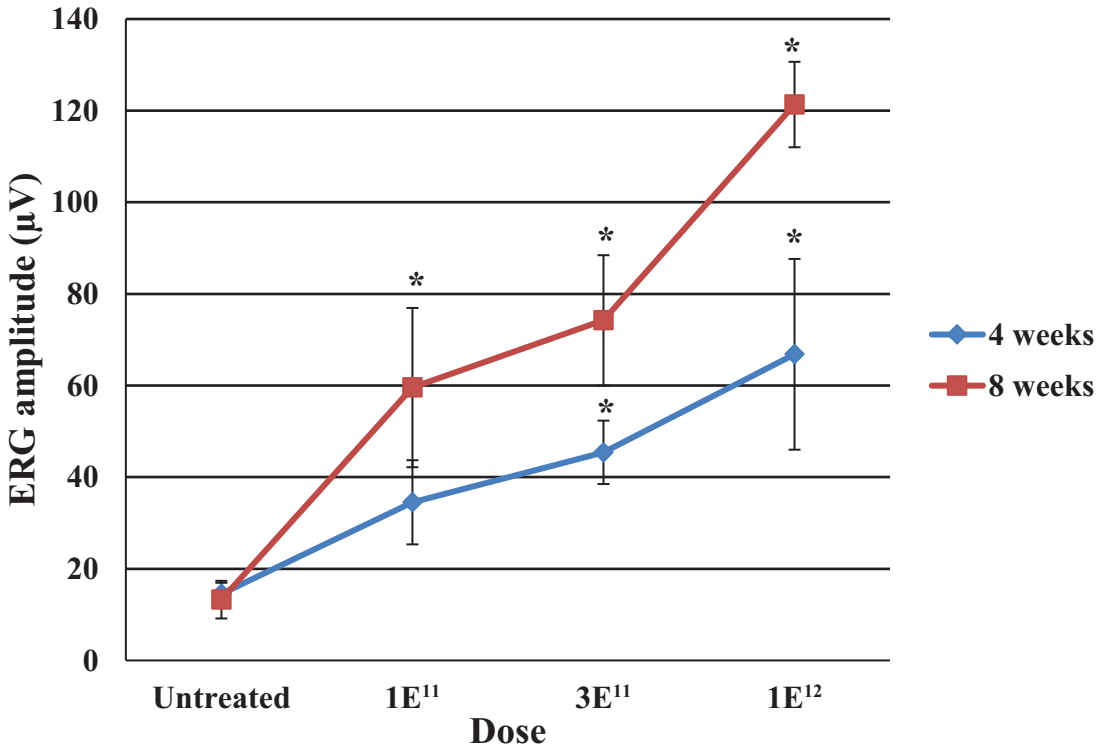


Figure 3. Graph of averaged photopic ERG amplitudes at four and eight week time-points post administration of AAV-CNGB in *Cngb3* mutant mice treated at four weeks of age. The blue line indicates the electrical response amplitudes observed following administration of different doses of AAV-CNGB3 measured at four weeks after treatment. The red line shows the increased level of electrical response observed in the same mice treated with AAV-CNGB3 four weeks later, at eight weeks following treatment. This is compared to the ERG response in untreated eyes, which remained unchanged at both time points.

During 2016, we conducted three preclinical toxicology studies of AAV-CNGB3 at UCL IO. We conducted a nine-month study in normal mice in which four eyes were dosed with saline as a control, nine eyes were dosed at $2E^9$ vg/eye, and nine eyes were dosed at $4E^9$ vg/eye, with a toxicology assessment at one, three, six and nine months post-administration. We also conducted an eight week study in normal mice, in which 15 mice were dosed with saline as a control, 15 mice were dosed at $2E^9$ vg/eye, and 15 mice were dosed at $4E^9$ vg/eye, providing five mice from each group for studying local and systemic effects at each time-point of one, four and eight weeks after treatment. We also conducted an eight week rabbit study in which the right eyes of nine animals were dosed with saline as a control, the right eyes of nine animals were dosed at $0.8E^{11}$ vg/eye and the right eyes of nine animals were dosed at $2.4E^{11}$ vg/eye, providing three animals from each dose group for studying local and systemic effects at each time-point of one, four and eight weeks after treatment. Biodistribution was examined in the eight-week mouse and rabbit studies. No harmful effects on the retina or systemically were observed at the time-points listed after treatment. The data from these studies have not been published. We used these data to support our clinical trial application, or CTA, and IND for treatment of patients with ACHM related to *CNGB3* mutations with AAV-CNGB3.

Clinical Development of AAV-CNGB3

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 (visual acuity, contrast sensitivity, mobility maze and photoaversion assessments), retinal imaging (color fundus photography, fundus autofluoresence imaging, spectral domain optical coherence tomography and visual field

testing) and electrophysiological assessments. The study center is the Moorfields Eye Hospital in London. We believe access to these ACHM patients has enabled us to efficiently enroll the most appropriate patients into our *CNGB3* Phase 1/2 clinical trial. We intend to present this natural history data to regulatory agencies for discussion of our pivotal trial design and path to regulatory approval. 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 trial in a condensed timeframe.

We are conducting a Phase 1/2 clinical trial of AAV-CNGB3 in both adult and pediatric patients. In the dose escalation phase of the trial, up to 18 adult patients (18 years or older) may be administered one of three different doses of vector in dose escalating cohorts of three to six patients at a time. We have treated patients in all three dose cohorts. We have also treated one pediatric patient in the expansion cohort of the trial. We will close out this trial six months after the last pediatric patient has been treated. Six months following treatment, each patient moves 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.

The primary endpoint of this open-label, dose-escalation clinical trial is the safety of a one-time subretinal administration of AAV-CNGB3 in patients with ACHM caused by *CNGB3* mutations. Secondary endpoints include the outcomes of a range of functional assessments and detailed structural analysis of the retina, including imaging of individual photoreceptors.

This trial is open in the United Kingdom and the United States. We have treated 11 adult patients, including three patients at the highest proposed dose, and nine pediatric patients.

We submitted our IND for AAV-CNGB3 to the FDA in the fourth quarter of 2017. The IND was initially not opened because we received a question from the FDA regarding our injection device compatibility assay, thus putting the IND on clinical hold until we satisfactorily answered the FDA's question and the clinical hold was lifted by the FDA. In the device compatibility assay the FDA noted a disparity between the target titer for the intended low dose dilution and the actual titer obtained on polymerase chain reaction, or PCR, analysis. The FDA requested clarification on whether this was an imprecise dilution scheme for the low dose or a PCR assay issue. We submitted a response to the FDA on May 2, 2018 providing data that identified the issue as a PCR assay artifact and also showing data that we believe supports that this has now been addressed. On May 31, 2018 the FDA released the clinical hold on our IND for AAV-CNGB3.

In this trial, AAV-CNGB3 viral vector is 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, which is the eye assessed to be the worst eye at baseline. We completed the dose escalation phase of our Phase 1/2 clinical trial, with 11 adult patients treated. These 11 patients were dosed in three cohorts with escalating doses of $1E^{11}$ vg/mL (cohort one), $3E^{11}$ vg/mL (cohort two) and $1E^{12}$ vg/mL (cohort three) of AAV-CNGB3. In addition, nine pediatric patients have now been treated in the extension phase of the study.

In each of the 11 adult patients treated and nine pediatric patients treated, the macula, including the fovea, was covered by the subretinal injection. Subretinal injections have been administered by three different surgeons at the Moorfields Eye Hospital in London and the University of Michigan Kellogg Eye Center in the United States.

In adult and pediatric *CNGB3* patients, treatment of the central retina with our AAV-CNGB3 product candidate via subretinal injection has been generally well tolerated. Data from the first adult treatment cohort along with our preclinical data of AAV-CNGB3 was used to support our PRIME designation that was awarded by the EMA in February 2018.

As of December 31, 2018, we had completed dosing of eleven adult patients and nine pediatric patients. We may treat up to four additional patients in the United States during the first quarter of 2019. We

expect to release data from the adult dose escalation cohorts along with preliminary six-month data from the pediatric patients in the second half of 2019.

Our *CNGB3* gene therapy product candidate, AAV-CNGB3, was granted orphan drug designation by the FDA and EMA, 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 to improve visual function. We have also been granted PRIME designation by the EMA.

ACHM Caused by Mutations in CNGA3

We are also developing AAV-CNGA3 to treat ACHM caused by mutations in the *CNGA3* gene. While the mechanism for treating *CNGA3* related ACHM is similar to that for *CNGB3*, we believe a larger amount of CNGA3 protein is required to restore cone function compared to CNGB3. We believe this may reflect the 1:3 ratio in which CNGB3: CNGA3 subunits associate to form the cone CNG channel. We have designed a synthetic promoter to drive high levels of CNGA3 expression specifically in cones. In preclinical studies, our novel cone specific promoter has been associated with strong gene expression in all human cone subtypes in human retinas grown *in vitro* using human pluripotent stem cells, or hPSC. 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.

A key aspect of developing an effective treatment for ACHM caused by *CNGA3* mutations is a promoter that drives robust gene expression in all of the three different cone subtypes, S/blue, L/red and M/green. In particular, it is important to evaluate the activity of the promoter in human photoreceptors, which can be achieved prior to treating patients using human stem cell derived retinas. Our relationship with UCL provides access to what we believe is one of the few centers in the world that can generate human “mini retinas,” or HMRs, which are human retinas grown *in vitro* from hPSCs. These HMRs develop from stem cells over several months to form primary photoreceptors arrayed in a spherical structure that resembles many aspects of the human retina and includes all the rod and cone subtypes, allowing us to assess and predict the utility of many aspects of gene therapy vectors for human clinical application.

In vitro studies to measure the gene expression driven by our cone specific promoter in human cones using HMRs were conducted at UCL IO during 2017. Figure 4A shows a fully formed HMR that has been transfected with a construct in which our cone specific promoter was associated with the expression of green fluorescent protein, or GFP, a green marker gene. The expression of GFP is seen specifically in cone photoreceptors throughout this HMR, indicating that our promoter is driving robust gene expression in human cones. To support that this promoter drives gene expression in all cone subtypes, GFP expression driven by our promoter was overlaid with markers specific to each of the cone types. Figure 4B is an image of an S/blue cone and Figure 4C is an image of an L/red cone and an M/green cone, with the cone-specific marker labeled in red in each case. The multiple colors in Figures 4B’ and 4C’ show the overlay of these cone-specific markers with cone specific GFP expression, indicating that our promoter drives gene expression in all cone subtypes in this HMR. The data from these studies have not been published.

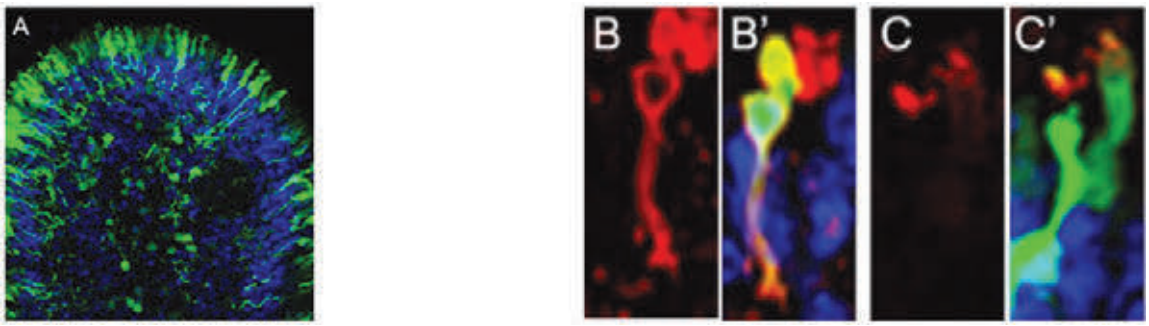


Figure 4A. An hPSC derived HMR showing GFP expression (green) driven by our promoter in human cones throughout the HMR.

Figure 4B. The red marker identifies this cone as an S/blue cone.

Figure 4B'. An overlay of GFP expression from our promotor on top of the S/blue cone specific marker. The overlap between the cone marker and GFP expression indicates that our promoter drives gene expression in S/blue cones.

Figure 4C. The red marker identifies M/red and L/green cones.

Figure 4C'. An overlay of GFP expression from our promotor on top of the M/Red and L/green cone specific marker. The overlap between the cone marker and GFP expression indicates that our promoter drives gene expression in M/red and L/green cones.

In preclinical studies of mutant mice lacking the *Cnga3* gene conducted at UCL IO during 2017 and 2018, treatment of retinas of *Cnga3* mutant mice with AAV-CNGA3 was associated with restoration of the cone electrical response following subretinal delivery. Figure 5 and Figure 6 show the rescue of cone function that was observed in two of these studies with doses spanning those proposed in the clinical trial and in a dose dependent manner. We believe this supports the evaluation of AAV-CNGA3 to treat patients with ACHM caused by mutations in *CNGA3* in a Phase 1/2 clinical trial. The data from these studies have not been published.

Figure 5 shows the electrical response of retinas to a single flash of bright light. A retina from three different mice were tested: a normal mouse (Figure 5A), a mutant mouse lacking the *Cnga3* gene (Figure 5B) and a mutant mouse lacking the *Cnga3* gene, but treated with 3uL of $1E^{12}$ vg/mL AAV-CNGA3 (Figure 5C). A high degree of restoration of function of mutant cones was observed in the retina from the *Cnga3* mutant mouse treated with AAV-CNGA3, with approximately 60% of the electrical response to a bright flash of light of the normal retina observed in the retina from the *Cnga3* mutant mouse that were treated with AAV-CNGA3. The mice were injected with AAV-CNGA3 at four weeks of age and assessed using ERG four weeks post injection.

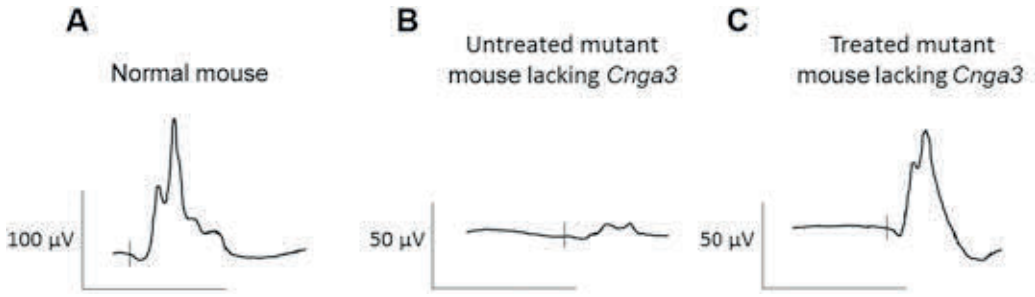


Figure 5. Cone electrical response in mice retinas reacting to a single flash of bright light, measured by ERG.

Figure 5A. The electrical response of the retina from a normal mouse reacting to a flash of bright light.

Figure 5B. The electrical response of the retina from a mutant mouse lacking *Cnga3* reacting to a flash of bright light.

Figure 5C. The electrical response of the retina from a mutant mouse lacking *Cnga3* treated with AAV-CNGA3 reacting to a flash of bright light.

Figure 6 shows the cone-mediated ERG responses measured in *Cnga3* mutant mice treated with three different doses of AAV-CNGA3. 3uL of AAV-CNGA3 was administered via subretinal injection in each eye at $1E^{11}$ vg/mL (n=5), $3E^{11}$ vg/mL (n=5) and $1E^{12}$ vg/mL (n=5). The mice were treated at 15 days old and the ERG was measured four weeks after treatment. The reviewer analyzing the ERG responses was masked to which eye received treatment. Doses tested in this study span the doses of AAV-CNGA3 proposed for our Phase 1/2 clinical trial. Figure 6 shows the ERG responses that were observed at each of the three doses.

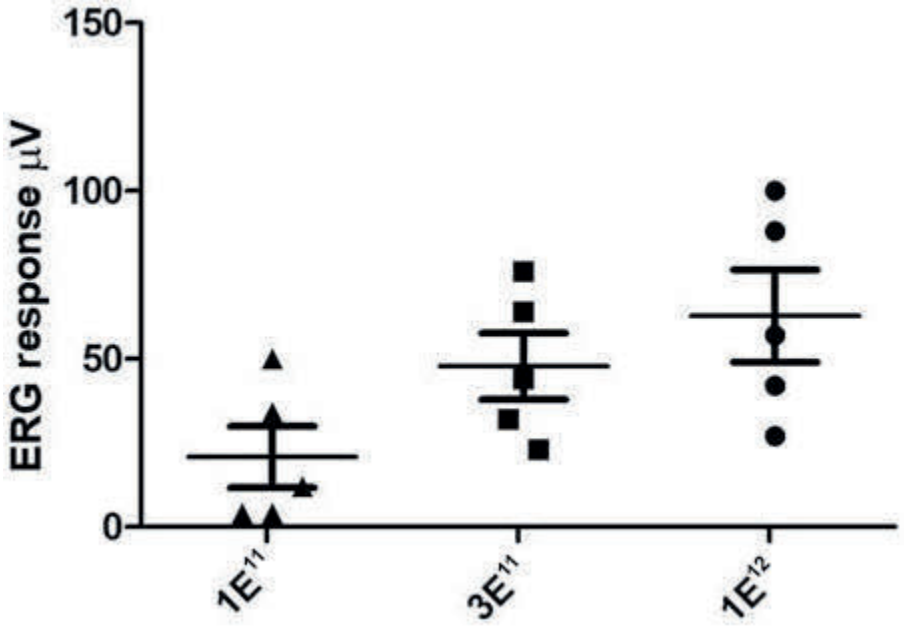


Figure 6. The photopic ERG amplitudes measured to assess cone photoreceptor function in *Cnga3* mutant mice treated with AAV-CNGA3 at doses of $1E^{11}$ vg/mL (n=5), $3E^{11}$ vg/mL (n=5) and $1E^{12}$ vg/mL (n=5). Mice were treated at 15 days post-natal and ERGs were assessed four weeks following treatment. The retinal ERGs are the electrical recordings corresponding to cone activity following a single pulse of bright light. A dose response was observed in retinal sensitivity obtained using the three tested doses and a treatment effect was also observed in the lowest dose tested.

In 2018, we completed a toxicology package similar to that used with the AAV-CNGB3 and AAV-RPGR programs using cGMP AAV-CNGA3 material manufactured at our cGMP facility. We conducted an approximately six-month toxicology study in mice and two, eight-week acute toxicology and biodistribution studies in mice and rabbits.

Clinical development of AAV-CNGA3

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

(visual acuity, contrast sensitivity, mobility maze and photoaversion assessments), retinal imaging (color fundus photography, fundus autofluoresence imaging, spectral domain optical coherence tomography and visual field testing) and electrophysiological assessments. The study center is the Moorfields Eye Hospital in London. We believe access to these ACHM patients will enable us to efficiently enroll appropriate patients into our *CNGA3* Phase 1/2 clinical trial. In addition to giving us access to patients and potentially accelerated enrollment in our treatment study, we believe the prospective natural history data on each treated patient will allow us to gather robust data from our Phase 1/2 clinical trial in a condensed timeframe.

We aim to initiate a Phase 1/2 dose escalating trial of AAV-CNGA3 in ACHM patients with mutations in *CNGA3*. AAV-CNGA3 clinical material is currently being manufactured at our cGMP facility and we expect to release material for this trial in the first half of 2019 and open a Phase 1/2 dose escalation trial in pediatric patients shortly thereafter.

We will present pre-clinical data describing our AAV-CNGA3 vector optimization work in a scientific forum in the first half of 2019.

X-Linked Retinitis Pigmentosa

Disease Background and Market Opportunity

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. There are currently no approved treatments for RP. We believe gene therapy is a promising therapeutic approach. 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. RP has an estimated prevalence of one in 3,500 in the United States, and between 10% and 15% of RP patients are estimated to suffer from XLRP. 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, Japan and EU5, with a little less than 50% 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.

The RPGR protein has an essential role in the maintenance of the structure and function of both rod and cone photoreceptors. The RPGR protein is tightly localized in the photoreceptors at the junction of the inner and outer segments, or cilium, of the photoreceptors. Correct localization of the RPGR protein to this site is important for the transport of light sensing proteins to the outer part of the photoreceptors, where these proteins convert light signals into electrical signals. In the absence of the RPGR protein the movement of light sensing protein within both rods and cones is impaired, leading to dysfunction and death of photoreceptors, resulting in retinal degeneration and ultimately complete blindness.

Our Gene Therapy Program

Our product candidate for the treatment of XLRP, AAV-RPGR, is designed to treat XLRP caused by mutations in *RPGR*, the most common form of XLRP. The eye specific form of RPGR is encoded by a nucleotide sequence called RPGR open reading frame 15, or *RPGR-ORF 15*. Both rods and cones photoreceptors require *RPGR-ORF 15* to function. The protein coding message *RPGR-ORF 15* contains a region of repeated

sequences that make the *RPGR-ORF 15* nucleotide sequence unstable in the cell. We have engineered a small deletion in *RPGR-ORF 15* that we observed was associated with a stable sequence that rescued RPGR protein levels, localization and function in mouse and human photoreceptors in preclinical studies. Our novel AAV-RPGR viral vector utilizes the human rhodopsin kinase, or RK, promoter to specifically drive the expression of our stabilized *RPGR-ORF 15* in both rods and cones. We selected the AAV5 capsid because of its efficient transfection into both of these types of photoreceptors.

In preclinical studies, performed at UCL IO between 2009 and 2015 and discussed in *Gene Therapy* in 2016, it was observed that treatment with AAV-RPGR containing our stabilized *RPGR-ORF15* was associated with rescue of the *Rpgr* mutant phenotype in mice that completely lacked the RPGR protein as measured by ERG responses of retinas from *Rpgr* mutant mice and assessments of RPGR protein. Restored levels, localization and function of RPGR protein in mutant mice lacking the *Rpgr* gene were observed, along with the restoration and localization of photosensitive proteins in both rod and cone photoreceptors, and reduction of long-term retinal degeneration. In addition to these experiments in *Rpgr* mutant mice, we have observed that our *RPGR-ORF 15* construct also rescued levels, localization and function of RPGR protein in human photoreceptors, in HMRs derived from patients with *RPGR* mutations. We believe that AAV-RPGR may have the potential to positively impact human photoreceptor function and survival in XLRP-RPGR patients, slowing or halting the degeneration that leads to blindness in these patients.

Figure 7 and Figure 8 show data from these preclinical studies regarding the effect of subretinal delivery of AAV-RPGR containing our stabilized *RPGR-ORF 15* in mice lacking the *Rpgr* gene. In these studies, different color stains were used to investigate the restoration of (i) RPGR protein expression, (ii) correct localization of RPGR protein and (iii) RPGR function. Figure 7 and Figure 8 show a retina from a normal mouse (7A and 8A), a retina from a mutant mouse strain lacking the gene for *Rpgr* (7B and 8B) and a retina from the same mutant mouse strain that lacks the gene for *Rpgr*, but treated with AAV-RPGR containing our stabilized *RPGR-ORF 15* (7C and 8C).

The red stain in Figure 7 marks a photoreceptor protein, rootletin, within the cilium, or middle section, of every photoreceptor, while the green stain reveals the localization of RPGR protein. The green stain in Figure 7A shows the localization of RPGR protein within the photoreceptor at the end of the cilium in a normal mouse retina. Figure 7B shows a retina from a mouse lacking the *Rpgr* gene without any green staining, indicating the absence of the RPGR protein. Figure 7C shows a retina from a mouse lacking the *Rpgr* gene that was treated with AAV-RPGR containing our stabilized *RPGR-ORF 15*. The green staining at the end of the photoreceptor cilium is similar to the normal mouse retina. Treatment with AAV-RPGR containing our stabilized *RPGR-ORF 15* was associated with the restoration of RPGR protein expression and localization within the individual photoreceptor cells consistent with normal RPGR expression.

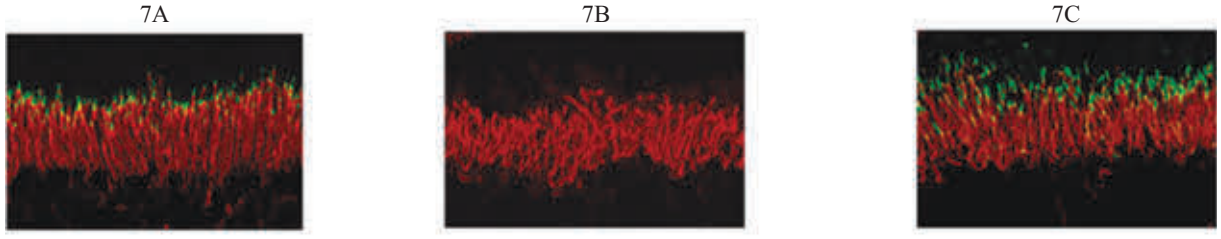


Figure 7. In these preclinical mouse models, the red staining marks a normal protein in the photoreceptor cilia, rootletin, while the green stain reveals localization of RPGR protein within the photoreceptor.

Figure 7A. The retina from a normal mouse.

Figure 7B. The retina from a mouse completely lacking the *Rpgr* gene.

Figure 7C. The retina from a mouse completely lacking the *Rpgr* gene and treated with AAV-RPGR containing our stabilized *RPGR-ORF 15*. The green stain indicates that RPGR protein expression was restored and was similarly localized within the individual photoreceptor consistent with normal RPGR expression.

Figure 8 shows a different analysis of retinas from the same mutant mouse strain that completely lacks the gene for *RPGR* expression. This analysis uses a yellow tag to reveal the location of photoreceptor light pigment, or opsins. The top row shows the rod opsin (8A; 8B; 8C), rhodopsin, and the bottom row shows cone opsin (8A[1]; 8B[1]; 8C[1]). Fully functional RPGR is critical for the correct localization of opsins and Figures 8B and 8B[1] show that in a *Rpgr* mutant mouse retina the opsins are incorrectly localized. Figures 8C and 8C[1] show that treatment of these mutant animals with subretinal injection of AAV-RPGR containing our stabilized *RPGR-ORF 15* enabled the correct location of the opsins within the photoreceptor as seen in the similarity to the normal mouse, indicating that RPGR is functionally active in supporting correct localization of key photoreceptor proteins.

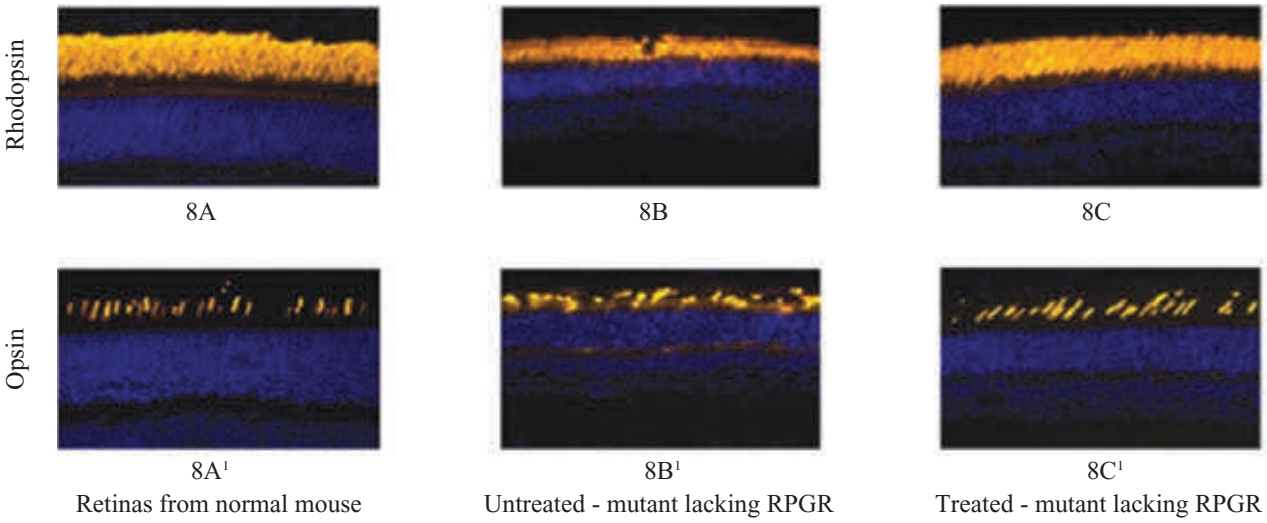


Figure 8. In these preclinical mouse experiments, a yellow tag reveals the location of the opsins.

Figures 8A and 8A[1]. Normal mouse retina showing the localization of rhodopsin and opsin.

Figures 8B and 8B[1]. *Rpgr* mutant mouse retina showing the localization of rhodopsin and opsin.

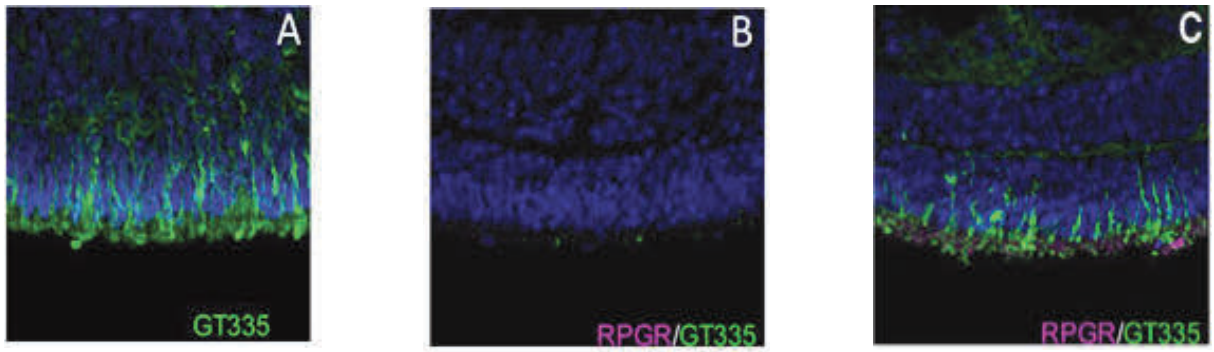
Figures 8C and 8C[1]. *Rpgr* mutant mouse retina that was treated with AAV-RPGR containing our stabilized *RPGR-ORF 15* shows the localization of rhodopsin and opsin. The similar localization between the normal mouse retina and the *Rpgr* mutant mouse retina that was treated with AAV-RPGR containing our stabilized *RPGR-ORF 15* indicates that the rhodopsin and opsin are correctly localized and can perform their key function in the visual cycle.

We are further advancing the HMR system to evaluate the potential for our product candidates to functionally restore mutant photoreceptor cells in a human retina.

One of the many tasks that *RPGR* performs in the photoreceptor is to enable a process called glutamylation of a key cilia protein called tubulin, which is required for photoreceptor function. We conducted an *in vitro* study at UCL IO in 2016 using HMRs derived from stem cells from XLRP-RPGR patients to determine the effect of AAV-RPGR containing our stabilized *RPGR-ORF 15* on human photoreceptors. The data from this

study has not been published. An HMR grown from hPSC from a normal individual is shown in Figure 9A, in which glutamylation of tubulin in normal human photoreceptors is stained in green. Figure 9B shows a HMR derived from a XLRP-RPGR patient and cultured over several months to form many of the anatomic layers of the retina and consisting of all photoreceptor types, while Figure 9C shows the impact of AAV-RPGR containing our stabilized *RPGR-ORF 15* treatment on a similarly cultured HMR derived from a XLRP-RPGR patient.

The HMR derived from a XLRP-RPGR patient lacks RPGR protein, making the photoreceptors dysfunctional with no glutamylation of tubulin present (Figure 9B). When HMRs from a XLRP-RPGR patient were treated with AAV-RPGR containing our stabilized *RPGR-ORF 15* we observed that glutamylation of tubulin returned (Figure 9C). We also stained HMRs derived from an XLRP-RPGR patient with a pink marker of RPGR protein. In Figure 9B no pink staining was observed, confirming the lack of RPGR protein. In Figure 9C, when the HMR from a XLRP-RPGR patient was treated with AAV-RPGR containing our stabilized *RPGR-ORF 15*, pink staining can be seen at the correct localization in the base of the cilium of the photoreceptors that are now stained with green glutamylation of tubulin marker. This restoration of RPGR protein expression and localization, and restoration of markers of photoreceptor function in human photoreceptors in HMRs derived from XLRP-RPGR patients, indicates potential clinical utility of AAV-RPGR containing our stabilized *RPGR-ORF 15*.



Derived from normal patient

Untreated - Derived from XLRP-RPGR patient

Treated - Derived from XLRP-RPGR patient

Figure 9. A HMR derived from hPSCs from a normal individual (9A) or a XLRP-RPGR patient (9B and 9C) cultured over several months to form many of the anatomic layers of the retina and consisting of all photoreceptor types with the glutamylation of tubulin having a green fluorescent stain.

Figure 9A. A HMR derived from normal hPSCs.

Figure 9B. A HMR derived from a XLRP-RPGR patient.

Figure 9C. A HMR derived from a XLRP-RPGR patient that was treated with AAV-RPGR containing our stabilized *RPGR-ORF 15*. The appearance of pink RPGR protein at the base of the photoreceptor cilium and glutamylation of tubulin returns, demonstrating the restoration of RPGR protein expression, localization and function.

To support the advancement of AAV-RPGR into clinical development, we conducted three single-dose toxicology studies from January 2016 to August 2017 at UCL IO. We performed a six-month toxicology study in normal mice delivering doses of saline in both eyes for the control (n=5), and doses of AAV-RPGR in both eyes of $2E^9$ vg/eye (n=5) and $4E^9$ vg/eye (n=5), with a toxicology assessment at one, three and six months post-administration. Two further toxicology studies were performed. An eight week mouse study in which groups of mice were dosed with saline in both eyes as a control (n=15), AAV-RPGR in both eyes at $1E^9$ vg/eye (n=15) or AAV-RPGR in both eyes at $4E^9$ vg/eye (n=15), providing five mice from each group for studying local and

systemic effects at each time-point of one, four and eight weeks after treatment. An eight-week rabbit study was also conducted, in which nine right eyes were dosed per group, with doses of saline as a control, and AAV-RPGR doses of $0.8E^{11}$ vg/eye and $2.4E^{11}$ vg/eye, providing three rabbits for studying local and systemic effects at each time-point of one, four and eight weeks after treatment. Biodistribution was examined in the eight-week mouse and rabbit studies. No harmful effects on the retina or systemically were observed. We used these data to support our CTA and IND for treatment of XLRP-RPGR patients with AAV-RPGR.

Clinical Development of AAV-RPGR

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 (visual acuity and contrast sensitivity), retinal imaging (color fundus photography, fundus autofluoresence imaging, spectral domain optical coherence tomography, adaptive optics and visual field testing) and electrophysiological assessments. The study centers are the Moorfields Eye Hospital in London, the Kellogg Eye Center at the University of Michigan, the Medical College of Wisconsin & Froedtert Hospital and Massachusetts Eye and Ear. We believe access to this large population of XLRP-RPGR patients has enabled us to efficiently enroll appropriate patients into our XLRP-RPGR Phase 1/2 clinical trial. 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 will potentially allow us to enroll a more heterogenous population into our treatment studies and may allow us to gather robust data from our Phase 1/2 clinical trial in a condensed timeframe.

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. 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 to prevent this ultimate degeneration to blindness and to retain visual acuity, the central region of the retina, including the macula and fovea, must be preserved. To this end, we aim to deliver AAV-RPGR to this central region of the retina. In our Phase 1/2 clinical trial, AAV-RPGR viral vector is 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. One eye is treated in each patient, which is the eye assessed to be the worst eye at baseline.

We are conducting a Phase ½ clinical trial of AAV-RPGR in both adult and pediatric XLRP-RPGR patients. This trial is open in the United Kingdom under our CTA and in the United States under our IND.

We have treated ten young adult patients (aged 18 to 30 years old) in the Phase 1/2 XLRP-RPGR clinical trial. We have treated one pediatric patient in the pediatric extension arm of this trial. We expect to treat up to 40 additional patients in the extension cohorts of this study in 2019. In all patients, subretinal injection covered the central part of the retina, including the macula and fovea.

We expect to report preliminary safety and efficacy data from the dose escalation cohorts in the second half of 2019.

The FDA and EMA have granted orphan status to AAV-RPGR for the treatment of retinitis pigmentosa. The FDA has also granted Fast Track designation to AAV-RPGR for the treatment of XLRP caused by defects in *RPGR.*

RPE65-Deficiency

Disease Background and Market Opportunity

RPE65-deficiency causes rod photoreceptor dysfunction and impaired vision from birth. The *RPE65* gene encodes a protein that is produced in the retinal pigment epithelium, or RPE, a thin layer of cells at the back of the eye that support photoreceptors and nourish the retina. The RPE65 protein is essential for rod function because it recycles the light sensing machinery in rod photoreceptors. 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*-deficient patients experience central vision loss progressing to complete blindness by early adulthood.

RPE65-deficiency is often characterized as a specific subtype of Leber congenital amaurosis or RP that is caused by mutations in the *RPE65* gene, called Leber congenital amaurosis 2 and RP20, respectively. However, we believe a more precise approach to genetic diseases is to focus on the underlying genetic defect, rather than the phenotype, and have therefore identified *RPE65*-deficiency as the target of our product candidate AAV-RPE65.

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 believe the availability of a therapeutic option may increase patient identification and estimated prevalence of *RPE65*-deficiency.

Our Gene Therapy Program

Our gene therapy candidate for the treatment of *RPE65*-deficiency, AAV-RPE65, is an AAV2/5 viral vector, in which a codon optimized *RPE65* gene is driven by a novel synthetic RPE cell specific promoter.

RPE65-deficiency is a well validated condition for gene replacement therapy. In multiple clinical trials, including one conducted by our collaborators at UCL, replacing the mutant *RPE65* gene with a normal copy of the gene resulted in improved nighttime vision in affected children and young adults, suggesting the potential impact of gene therapy on rod function in this disease. The FDA recently approved the first gene treatment for *RPE65*-deficiency, Luxturna. While *RPE65*-deficiency 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.

We focus on detailed structural and functional data in our treatment studies with the aim of demonstrating an impact on the degeneration of the central retina.

Our novel AAV2/5 vector, AAV-RPE65, has been optimized for both transduction of RPE cells and RPE65 protein production and our surgical approach targets the central area of retina whose preservation is most critical for long term maintenance of visual function. Building on the work of Professor Ali and in collaboration with the team at UCL, we have developed AAV-RPE65. AAV-RPE65 is a second generation viral vector that has compared favorably to our first generation AAV2/2 vector in a number of ways, including being two to three logs, or 100 to 1,000 times, more potent on a particle for particle basis than our original AAV2/2 vector in a head

to head *Rpe65* null animal model rescue experiment. On a logarithmic scale, each "log" represents a 10-fold change. We believe this increased potency will improve transgene expression and RPE65 protein production in the back of the eye. The table below summarizes elements of the optimization of AAV-RPE65 compared to our original AAV2/2 vector. Vector optimization studies were performed at UCL IO and were carried out from 2010 to 2015. The data summarized here was referred to in *Gene Therapy* in 2016. We used these data to support our IND and CTA for treatment of *RPE65*-deficient patients with AAV-RPE65.

Optimization of AAV2/5 compared to AAV2/2	
Transfection Efficiency	Changing the capsid from AAV2/2 to AAV2/5 was associated with an improvement of the transfection efficiency of RPE by four times.
Protein Expression (Promoter)	AAV2/5's optimized promoter was associated with a 20 times increase in protein expression.
Protein Expression (Codon)	AAV2/5's optimized codon usage was associated with a seven times increase in protein expression in human cells.
mRNA Stability	Utilizing SV40 intron increases mRNA stability and was associated with a two and one half times increase in protein production.
Overall Efficacy	The optimized construct was associated with a 300 to 1,000 times increase in efficacy in mouse functional rescue and is expected to be two to three logs more potent on a particle for particle basis in humans.

We conducted four single-dose toxicology and biodistribution studies of AAV-RPE65 from January 2015 to December 2016. We performed a long-term toxicology study in normal mice in which four eyes were dosed with saline as a control and nine eyes were dosed with AAV-RPE65 at $4E^9$ vg/eye, with a toxicology assessment at one, three, six and nine months post-administration. We also conducted an eight-week mouse study, an eight-week rabbit study and an eight-week minipig study. In the mouse study, 15 mice were dosed in both eyes with saline as a control, 15 mice were dosed in both eyes with AAV-RPE65 at $1.2E^9$ vg/eye and 15 mice were dosed in both eyes with AAV-RPE65 at $3.7E^9$ vg/eye, providing five mice from each group for studying local and systemic effects at each time-point of one, four and eight weeks after treatment. In the rabbit study, nine rabbit's right eyes were dosed for each group with a saline control group, a $0.6E^{11}$ vg/eye group and a $1.9E^{11}$ vg/eye group, providing three animals from each group for studying local and systemic effects at each time-point of one, four and eight weeks after treatment. The minipig study was a two-week single dose injection study in minipigs (n=2, each dosed in one eye) at a dose of $1.84E^{10}11$ vg/eye. The minipig study was performed by Charles River Laboratories, while the other three studies were performed at UCL IO. No harmful effects on the retina were observed during these studies. We used these data in support of our CTA and IND for treatment of *RPE65*-deficient patients with AAV-RPE65.

Clinical development of AAV-RPE65

We have an ongoing natural history study in patients with *RPE65*-deficiency with approximately 30 patients enrolled that allows us to collect structural and functional data on prospectively defined endpoints, including functional tests (mobility maze, color vision, visual acuity and quality of life measures), retinal imaging (color fundus photography, fundus autofluoresence imaging, visual field testing, spectral domain optical coherence tomography and adaptive optics) and electrophysiological assessments. The study is global, with study centers including at the Moorfields Eye Hospital in London, University of Michigan Kellogg Eye Center and the Medical College of Wisconsin & Froedtert Hospital. We plan to present this natural history data to regulatory agencies in our meetings following completion of the Phase 1/2 clinical trial for discussion of our pivotal trial design and path to regulatory approval.

This clinical trial enrolled patients in the United Kingdom under our CTA, as well as the United States under our IND. Dosing in the Phase 1/2 clinical trial was completed June of 2018. The primary endpoint of this

open-label, dose-escalation clinical trial is the safety of delivering AAV-RPE65 through subretinal injection in patients with *RPE65*-deficiency. 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 escalating cohorts and six pediatric patients in the pediatric extension arm of the trial. Surgeries in this trial have been carried out in the United States at the University of Michigan Kellogg Eye Center and in the United Kingdom at the Moorfields Eye Hospital by three different surgeons. No differences in outcomes have been observed between the different surgeons.

In cohort one, three adults (aged 19, 20 and 20 years old) were administered up to 1mL of $1E^{11}$ vg/mL of AAV-RPE65 vector. In each patient, the central region of the retina was targeted. No serious adverse events or dose limiting events have been reported in this cohort as of the 18-month time point following vector administration.

In each patient treated in cohort one, we observed improvement or stability in central visual function following treatment compared to baseline and compared to the untreated fellow eye. Retinal sensitivity was measured with threshold static perimetry using Octopus 900 perimetry and visual field modelling and analysis, or VFMA. Observations at 18 months following vector administration in the first cohort have demonstrated a potential increase in retinal sensitivity by up to 40% from baseline. In contrast, we observed that the untreated eyes of patients in this cohort suffered a reduction in retinal sensitivity of up to 40%, which is in consistent with data from our parallel prospective natural history study of *RPE65*-deficient patients. In addition to the perimetry and VFMA data, improvements in time and error rate in mobility maze navigation have been observed in these patients at six and 12 months following treatment. However, this is preliminary data and needs to be supported by data collected at later time-points and in larger numbers of patients.

In addition to the functional data discussed above, we are collecting detailed structural data on all patients in our Phase 1/2 clinical trial. This includes data to visualize the mosaic of individual cones in the central part of the retina over time in each patient. As of May 4, 2018, we had sequential cone map data for more than 18 months following subretinal injections that covered the macula and fovea in the patients in cohort one and we had not observed retinal thinning or loss of cones over time following treatment. We are continuing to monitor the detailed structure of both treated and untreated fellow eye in the five-year follow on study to assess if AAV-RPE65 treatment has an impact on degeneration in the treated area of the eye compared to the untreated fellow eye.

In cohort two, three adults (aged 16, 20 and 22) were administered vector peripherally via subretinal injection into the outer region of the retina at a higher dose of up to 1mL of $3E^{11}$ vg/mL. Following completion of the four-week steroid taper, in two patients inflammatory responses were noted by the investigator as being probably related to vector administration. Both responded to a further course of steroids. Improvements in visual mobility in study eye over non-study eye were observed at 12 months at the four lux lighting level in this cohort. Similar increases in retinal sensitivity to cohort one have not been observed at this dose level. We believe data from cohort two is suggestive that peripheral administration of the vector into more degenerating areas of the retina may result in an increased chance of an immune response with a decreased potential benefit compared central administration of the vector. Following the review of the safety data for each adult cohort treated in this study, the IDMC recommended escalation to the higher dose in the next cohort.

Based on the safety and activity data from the patients treated at the $1E^{11}$ vg/mL dose level (cohort one), the decision was made to treat pediatric patients at this dose prior to receiving the full safety data from adult cohort three, and to target the central part of the retina in all pediatric patients. Treatment of pediatric patients in the United Kingdom and United States has been completed and six pediatric patients have been treated.

We carry out detailed assessments of retinal sensitivity across the entire retina, with the majority of tested retinal locations covering the central retina, at baseline and at prospectively defined time-points following

treatment using the Octopus 900 perimeter. The Octopus 900 perimeter, unlike other standard clinical devices, enables full-field static perimetry using testing algorithms specifically designed for retinal conditions, affords the use of custom-developed testing grids, and allows the full dataset to be extracted and modelled for more accurate measurement of change over time.

Discreet small spots of light are shone onto multiple predetermined points (the test grid) covering the central retinal field and peripheral retina, with the patient responding each time they perceive a spot of light. Each point on the retina is tested multiple times with different intensities of light, thereby allowing the determination of both the reliability and reproducibility of the patients' response to each light level at each spot and an accurate measurement of the exact retinal sensitivity at topographically determined points. The data is read out as a 'heat map' of sensitivity across the retinal field. The reliability of the patient and the data produced is also calculated and provided by the machine. In addition to the heat map of retinal sensitivity and conventional mean sensitivity metric produced by Octopus 900 assessment, we also conduct advanced VFMA. This produces a volumetric measure of retinal sensitivity presented both numerically as well as in a topographical retinal sensitivity map, which better represents the entire dataset across the visual field. We compare the VFMA data from the retinal map at each timepoint following treatment to the baseline data to measure the extent and position of changes in retinal sensitivity over time in treated and untreated eyes.

We completed dosing of the final pediatric patients in June of 2018, and we closed out the study six months after the last pediatric patient was treated. Patients will then move into a long term follow up study in which patients will be followed for safety and an indication of benefit for an additional four and a half years.

We expect to report topline six-month follow up safety and efficacy data in the first half of 2019, with full data expected to be presented in a scientific forum in the second half of 2019.

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

LCA4

Disease Background

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.

Our Gene Therapy Program

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. We believe we are well placed to initiate the first clinical intervention in this indication through our relationships with UCL and Moorfields Eye Hospital, whose expertise and large IRD patient population enables such an aggressive and uncommon IRD to be treated.

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.

Much of the preclinical work to support the proof of concept for gene therapy in LCA4 was conducted by our collaborators at UCL IO, led by Professor Robin Ali, and was published in *Gene Therapy* in 2010.

Figure 10 and Figure 11 show histological sections revealing the structure of retinas from *Aipl1* mutant mice treated with AAV-AIPL1, compared to untreated retinas from *Aipl1* mutant mice, at six months and 23 months after treatment.

It was observed at both time-points that *Aipl1* mutant mice treated with AAV-AIPL1 suffered less photoreceptor loss than untreated *Aipl1* mutant mice, with the retinas of untreated mutant mice almost completely degenerated by 24 months of age. *Aipl1* mutant mice were treated with.5uL of AAV-AIPL1 at $1E^{12}$ at four weeks post-natal and eyes were sectioned at six months and 23 months after treatment. These treated retinas were compared to retinas from untreated control *Aipl1* mice (n=17 eyes), and retinas from normal mice without the *Aipl1* mutation sectioned at the same post-natal ages as the treated *Aipl* mutant mice. The data indicates that subretinal administration of AAV-AIPL1 is associated with the protection of the retina from degradation that occurs in *Aipl1* mutant mice, and this effect was durable out to two years, the oldest age studied in these mice.

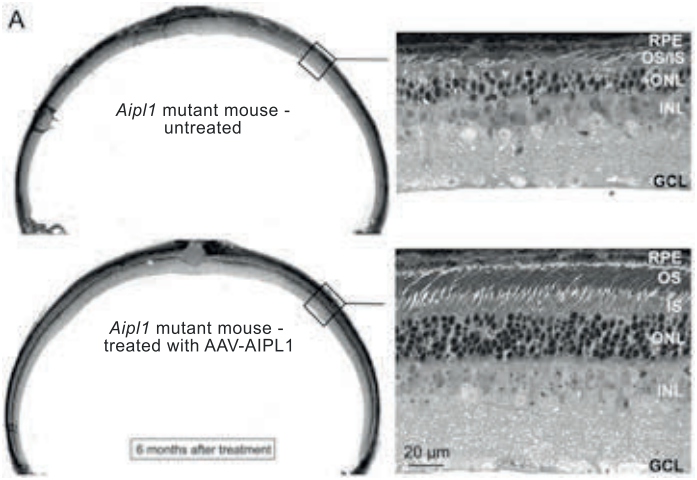


Figure 10. Histological sections of retinas of *Aipl1* mutant mice treated with AAV-AIPL1 six months after treatment with AAV-AIPL1, compared to untreated retina. The top image is the retina of an untreated *Aipl1* mutant mouse at seven months post-natal. The lower image is the retina of a *Aipl1* mutant mouse at seven months post-natal, and six months following treatment with AAV-AIPL1.

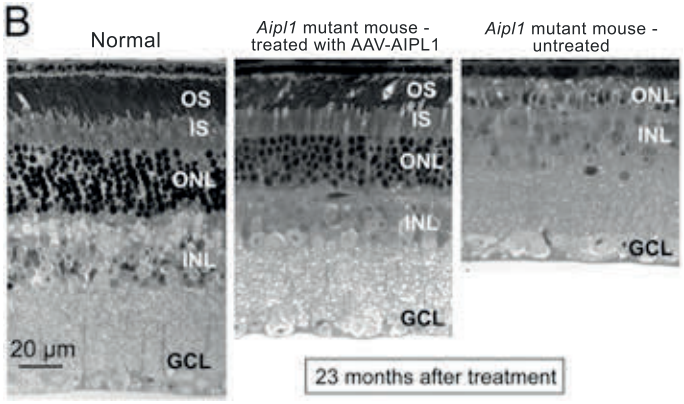


Figure 11. Histological sections of retinas of *Aipl1* mutant mice treated with AAV-AIPL1 23 months after treatment with AAV-AIPL1, compared to untreated retina and retina from a normal mouse. The left image

is the retina of an normal mouse at 24 months post-natal. The middle image is the retina of an *Aipl1* mutant mouse at 24 months post-natal, and 23 months following treatment with AAV-AIPL1. The right image is the retina of an untreated *Aipl1* mutant mouse at 24 months post-natal.

Clinical material was manufactured to cGMP standards under a specials license. Some of this clinical material was used in studies in 2017 at UCL to confirm potency in an AIPL1 deficient mouse and to perform toxicology testing in normal mice and rabbits. A potency study was conducted at a AAV-AIPL1 dose of $3E^9$ vg/eye with a group size of three eyes. Assessments were performed at three weeks and supported the potency of the cGMP clinical material through analysis of the ERG response.

A toxicology study was performed with normal mice and rabbits. In the mouse portion, five animals per group were evaluated for local and systemic effects at four weeks. In the rabbit portion, three animals per group were evaluated for local and systemic effects at four and eight weeks. Safety evaluation included functional assessments using ERG, fundoscopy, and structural assessments.

Our product candidate, AAV-AIPL1, was manufactured and released for compassionate use under a specials license in the UK to treat LCA4 patients at the Moorfields Eye Hospital. This allows physicians at the Moorfields Eye Hospital 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 the 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. Although patients have been reviewed at the Moorfields Eye Hospital, so far none have been treated with AAV-AIPL1. 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 UK's Medicines and Healthcare Products Regulatory Agency, or MHRA.

Manufacturing a special also imposes a five year record retention requirements 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 EMA granted orphan designation to our product candidate, AAV-AIPL1, for treatment of inherited retina dystrophy due to defects in *AIPL1* gene.

Age-Related Macular Degeneration (AMD)

Disease Background and Market Opportunity

AMD is a chronic eye condition that causes gradual decline of central vision. It is the leading cause of vision loss in individuals more than fifty years old in the United States and it affects 6.2 million people globally. Although AMD does not usually lead to complete blindness because peripheral vision is generally maintained, losing central vision has a critical impact on visual acuity, which is achieved by the closely packed cones of the central retina. As a result, loss of central retinal function has a significant impact on a person's independence and quality of life.

AMD is a complex disease attributed to several different causes. A number of genetic and environmental risk factors have been associated with the development of AMD. Two late forms of AMD have been characterized: geographic atrophy, or dry AMD, and neovascular AMD, or wet AMD. Dry AMD is characterized by the progressive, irreversible loss of many of the cell types in the retina, including the RPE, photoreceptors, and underlying capillaries of the macula, and causes a decline in central visual function. Wet AMD is defined by the growth and invasion of immature blood vessels from the underlying choroid into the retina. Leakage from these fragile blood vessels causes build-up of blood and fluid under the retina, leading to detachment of the RPE or retina and long-term scarring.

Current therapeutic options for AMD are limited. There is no approved therapy that impacts the 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.

Effective treatments for wet AMD are focused on blocking blood vessel growth, or angiogeneisis, that underlies the pathology of the disease. These wet AMD treatments specifically block the activity of vascular endothelial growth factor, or VEGF, one of the key drivers of angiogenesis. There are two approved anti-VEGF treatments on the market, ranibizumab, or Lucentis, and aflibercept, or Eyelea. These may be effective in some wet AMD patients, but require challenging dosing regimens that typically include intra-ocular injections every one to three months.

Our Gene Therapy Programs

Wet AMD

We aim to use a gene-based strategy to deliver an anti-angiogenic molecule to the retina and create a "local factory" that will deliver a continual supply of antiangiogenic molecules to the key parts of the eye. This would require a one-time injection procedure to deliver the gene therapy to the affected eye. We focus our blockade on the receptor involved in driving aberrant blood vessel growth and leakage, VEGF Receptor 2, or VEGFR2. Rather than depleting the VEGF ligand from the system we aim to block the receptor for that ligand preventing VEGF binding to the receptor and thereby preventing downstream pathology of wet AMD that is normally triggered by VEGF binding to VEGFR2. We use an anti-VEGFR2 antibody. In some rodent models the inhibition of the VEGFR2 with this antibody appears to have reduced long term toxicity as compared to the depletion of the VEGF ligand. Initial studies have identified a lead candidate that we have now moved from the research stage to formal preclinical development. We are also working to integrate our gene regulation technology with our wet AMD program. Our ultimate aim is to activate the anti-VEGFR2 antibody gene that we have installed in the eye with a small molecule applied topically with an eye drop. This could potentially allow for intermittent dosing of the antibody using an eye drop rather than an injection.

Dry AMD—Rod to Cone Program

To treat dry AMD, and specifically to treat patients with geographic atrophy in which the central part of the retina is irreversibly damaged, we are advancing a novel strategy to alter the very character of rod photoreceptors.

In advanced forms of dry AMD, central visual function is lost after the fovea and the larger central retina area has degenerated, and any residual vision is generally via the outer retina's rods. A critical characteristic of cones that allows for response to high light levels is that they recover rapidly after they are stimulated by light. In contrast to cones, rods work in low light levels and require longer exposure to trigger an impulse and are then much slower to recover to a state when they can respond again. Therefore, seeing via rods is slow and imprecise, whereas cones mediate acute high-resolution vision. By genetically engineering rods with molecules that will improve their speed of recovery and response to light, we aim to effectively transform a patch of rod photoreceptors to behave more like cones. This rod-to-cone transformation would potentially be achieved

by using localized gene therapy vector placement in the rod-rich peripheral retina to create a small patch or "pseudo fovea," where cone like behavior of rods would enable the patient's brain to fixate on a functional part of the peripheral retina and recover a more cone like response to higher light levels.

The proof of concept has already been achieved in animal models, with first generation molecules designed to speed up the visual cycle recovery times in rods. We will continue to develop and optimize these molecules using our screening systems to allow selection for sensitivity to natural high light intensities and for the high refresh rate required.

Xerostomia

Disease Background and Market Opportunity—RIX

Radiation induced xerostomia, or RIX, is a severe and debilitating long-term side effect of radiation treatment for head and neck cancer. There is not currently any FDA approved treatment for RIX. Worldwide, there are approximately 500,000 new cases of head and neck cancer diagnosed each year, with approximately 50,000 cases in the United States 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 40% 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 United States, with approximately 10,000 new cases each year. Severity of RIX is measured from grade 1 (mildest) to 4 (most severe). As these patients tend to be under the care of a physician and dentist and have access to some form of health insurance, we believe this is an accessible indication with much larger commercial potential than some genetic diseases that are currently targets of our gene therapy programs.

RIX is a frequent side effect of head and neck cancer treatment because the standard treatment of locally advanced head and neck cancer involves radiotherapy, which can cause irreversible damage to non-diseased tissues located near oral tumors, such as the salivary glands. The fluid secreting, or acinar cells, of the salivary glands are uniquely sensitive to radiation, are destroyed acutely on IR exposure and to a large extent do not regenerate, resulting in chronically reduced salivary output. Because saliva plays such a critical role in the physiology and protection of upper gastrointestinal, or GI, tract tissues, patients with chronic RIX suffer severe long-term complications of head and neck irradiation that has a significant impact on the patient's daily living. 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.

Our Gene Therapy Program—RIX

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-AQP1 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 IR 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-AQP1 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 1/2 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 doses of AAV-AQP1 between $4.8E^7$ and $5.8E^9$ pu/gland 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 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. Up to 18 adult patients may be administered doses of AAV-AQP1 between $3E^9$ and $6E^{11}$ viral particles per gland in dose escalation cohorts of three patients each. 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. We have completed dosing in the first cohort and second cohort, having treated six patients. This clinical trial is being conducted in conjunction with the National Institute of Dental and Craniofacial Research at the NIH Dental Clinic.

We expect to initiate an additional clinical trial at Memorial Sloan Kettering Cancer Center and up to five additional clinical sites in the United States in 2019.

The FDA granted orphan drug designation for AAV-AQP1 to treat symptoms of grade 2 and grade 3 late xerostomia from parotid gland hypofunction caused by radiotherapy for cancer of the oral cavity.

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-AQP1 vector. Supported by data from our preclinical studies and our ongoing RIX clinical trials, we are currently conducting IND-enabling studies of AAV-AQP1 for xerostomia caused by Sjogren's syndrome.

Neurodegenerative Diseases

We also have clinical stage, research and preclinical programs targeting neurodegenerative diseases, with a clinical program in Parkinson's disease and a research focus in ALS and Alzheimer's disease. In ALS and Alzheimer's disease, we aim to target what we believe is a central factor in the underlying cell biology of the diseases - RNA metabolism in ALS and endosomal trafficking dysfunction in Alzheimer's disease. 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.

Parkinson's Disease

Disease Background and Market Opportunity

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 Gene Therapy Approach

AAV-GAD is an investigational gene therapy product candidate 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 it is believed that increasing subthalamic nucleus GAD expression through gene therapy has the potential to result in normalization 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.

AAV-GAD Clinical Results

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, with a significant improvement in the off-medication motor section of the Unified Parkinson's Disease Rating Scale, or UPDRS, part 3 observed in treated patients compared to baseline. There was also a significant difference in the degree of improvement observed compared with patients in the sham arm. The primary outcome measure was the six-month change from baseline in double-blind assessment of off-medication UPDRS motor scores. 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, $p=0.04$). Significant difference in the response rate between groups were observed, with responders being defined as patients achieving a 9-point or more improvement in UPDRS, which may be deemed clinically meaningful. At six months, 50% of AAV-GAD treated patients were responders compared with only 14% of patients in the sham arm. At 12 months, response rates were 63% and 24%, in AAV-GAD and sham arms, respectively. 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 most commonly reported adverse events were transient mild or moderate headache (seven in treated arm vs. two in sham arm), nausea (six in treated arm vs. two in sham arm) and worsening of Parkinson's disease (zero in treated arm vs. four in sham arm). 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. This 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.

ALS

Disease Background and Market Opportunity

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.

One gene linked to ALS is the transactive response DNA-binding protein 43, or *TDP-43*. The TDP-43 protein is one of a number of proteins that binds to cellular RNA and regulates its function and stability. When *TDP-43* does not function normally, RNA regulation in the neurons loses its tight control and the motor neurons die. While mutations in *TDP-43* account for only about 0.5% of ALS cases, aggregates of TDP-43 protein are observed in motor neurons of more than 95% of all ALS patients, including both inherited and sporadic, and TDP-43 aggregation is a central feature of diseased motor neurons in ALS patients. *TDP-43*, therefore, may be a critical therapeutic target for the treatment of both sporadic and inherited forms of ALS. TDP-43 aggregates are also seen in approximately 50% of patients with frontotemporal dementia, or FTD, suggesting a potentially similar underlying mechanism of this neurodegenerative disease.

Our Gene Therapy Approach

Genetic approaches using yeast as the primary model system have been used to identify ways of protecting motor neurons from death in ALS. A genetic screen was conducted to look for activated genes that rescue the toxicity of TDP-43 aggregation. A group of fives genes that reduce TDP-43 toxicity, was identified including members of the nonsense mediated decay, or NMD, machinery, and two genes in particular: up frameshift protein 1, or *UPF1*, and up frameshift protein 2, or *UPF2*.

NMD is the quality control system regulating RNA processing and activity in all cells, and has additional and broader functions specifically in regulating RNA in neurons.

Over the past decade, increasing evidence suggests that motor neurons may be particularly vulnerable to defects in RNA regulation, which may be caused by a number of defects, including *TDP-43* aggregation. We believe that increasing the master quality control machinery for RNA processing, NMD, in motor neurons may improve the ability of motor neurons to survive in ALS.

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. We are currently conducting IND enabling studies in animal models and have observed the preservation of neurons and a positive impact on functional endpoints in Fus and TDP-43 neuronal cell cultures. Based on data from our non-human primate studies conducted in 2018, we have identified a

proprietary capsid for use in our AAV-UPF1 vector. We anticipate completing pre-IND activity in 2019 and aim to file an IND in the second half of 2019. We expect that AAV-UPF1 clinical material for the Phase 1/2 clinical trial will be manufactured at our cGMP manufacturing facility.

Alzheimer's Disease

Disease Background and Market Opportunity

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. Two biological pathways have been identified that are considered causes of Alzheimer's disease. They are identified as causative because mutations in genes that affect these pathways alone cause patients to develop the disease. The first causative pathway, identified in rare forms of early onset Alzheimer's disease, is the misprocessing of amyloid precursor protein, or APP, caused by genetic defects in *APP* itself and the APP processing proteins presenilin 1 and 2. The second causative pathway is related to the correct movement, or trafficking, of cellular protein which is controlled by a cell component called the endosome. Loss of function mutations in the endosomal protein sortilin-related receptor 1, or *SORL1*, have recently been shown to cause Alzheimer's disease.

The endosome is an organelle within the cell that is responsible for correctly directing protein trafficking to different sites within the cell as well as to the cell surface. In neurons, there is significant protein trafficking, particularly at dendrites or neuronal connections where the endosomal trafficking system regulates the movement of the cell signaling machinery that allows neurons to communicate with one another.

The molecular machine that drives endosomal protein trafficking is made up of a complex of proteins together called the retromer. The protein encoded by the Alzheimer's disease causing gene *SORL1* is a retromer component. *SORL1* and other components of the retromer complex are commonly deficient in Alzheimer's disease patients' brains. Defects in the endosomal trafficking pathway have also been implicated in other neurodegenerative diseases, including Parkinson's disease, ALS and frontotemporal dementia.

Our Gene Therapy Approach

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 Gene Regulation Platform

We are developing a potentially transformative technology designed to enable us to use small molecules to turn gene therapy product candidates on and off. 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, for example epoetin alfa, 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 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, and this is the basis of our gene regulation platform.

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 range of regulation. Using a small molecule we were able to switch the riboswitch containing gene on to levels greater than 1,000x higher than in the absence of the small molecule. 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.

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 Medicines and Health Products Regulatory Agency, or MHRA, in the UK, EMA and FDA standards. In the first quarter of 2018, we had our final MHRA certification inspection. In May 2018, we were granted a license to manufacture gene therapy product candidates in our cGMP compliant manufacturing facility by the UK Medicines and Healthcare products Regulatory Agency.

We believe our facility can supply all of 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 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 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. 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 40 highly trained multidisciplinary staff on our manufacturing team with backgrounds in manufacturing, managing and delivering gene therapy products.

We have identified and licensed a proprietary HEK293 cell line that is well characterized and that we have banked in 400 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 lack the T antigen component and are suitable for both the current 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.

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 1/2 clinical trials to treat ACHM related to *CNGB3* and *CNGA3*, respectively, a product candidate in Phase 1/2 clinical trials by Nightstar Therapeutics plc and a program AGTC is running to treat XLRP, as well as Luxturna, which is marketed by Spark Therapeutics, Inc. and has been approved to treat *RPE65*-deficiency. 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. 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, 2018, we own, have an exclusive license or co-exclusive license under, or an exclusive option to license 38 United States and foreign issued or allowed patents and 176 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 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 BLA.

Company-Owned Intellectual Property

We own six patent families relating to gene regulation platform technologies developed by us. The first patent family includes 22 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, Australia, Canada, China, Hong Kong, India, Japan, Brazil, Egypt, Indonesia, Israel, Republic of Korea, Malaysia, Mexico, New Zealand, Vietnam, African Regional IPO, Philippines, Singapore, South Africa and Eurasia. 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 20 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, Australia, China, India, Japan, Brazil, Egypt, Indonesia, Israel, Republic of Korea, Malaysia, Mexico, New Zealand, Vietnam, African Regional IPO, Philippines, Singapore, South Africa and Eurasia. Additional filings in Hong Kong and Canada will be made in due course. 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 20 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, Australia, China, India, Japan, Brazil, Egypt, Indonesia, Israel, Republic of Korea, Malaysia, Mexico, New Zealand, Vietnam, African Regional IPO, Philippines, Singapore, South Africa and Eurasia. Additional filings in Hong Kong and Canada will be made in due course. 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 19 pending patent applications with claims directed to compositions of matter and methods of use in the United States, Europe, Australia, India, Japan, Brazil, Egypt, Indonesia, Israel, Republic of Korea, Malaysia, Mexico, New Zealand, Vietnam, African Regional IPO, Philippines, Singapore, South Africa, and Eurasia. Additional filings in China, Hong Kong, and Canada will be made in due course. 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 other two families include two international applications relating to different gene regulations platform technologies with claims directed to compositions of matter and methods of use. We expect to convert each of these international applications to U.S. and international patent filings in due course. Patents issued from these two patent families are expected to expire in 2037 and 2038, not including any patent term adjustments that may extend the patent term in certain jurisdictions.

We also own one patent relating to a vector technology developed by Vector Neurosciences Inc, acquired on October 5, 2018, with claims directed to compositions of matter. This patent is expected to expire October 21, 2025, 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 49 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 18 pending patent applications in the United States, Europe, Australia, Canada, China, Hong Kong, India, Japan, Brazil, Egypt, Israel, Malaysia, Mexico, New Zealand, Nigeria, Philippines, Singapore, 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, with claims directed to compositions of matter and methods of use relating to our achromatopsia program and the AAV-CNGA3 product candidate, includes one pending patent application, which we expect to convert to an international application and subsequent U.S. and international patent filings in due course. Patents issued from this family are expected to expire in January 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 AAV-RPGR product candidate, includes one allowed patent application

in the United States and four pending applications in Europe, Canada, China, and Japan. Patents issued from this family are expected to expire in July 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 25 pending applications in the United States, Europe, Australia, Canada, China, Hong Kong (two applications), India, Japan, Brazil, Egypt, Indonesia, Israel, Republic of Korea, Malaysia, Mexico, New Zealand, Nigeria, Vietnam, African Regional IPO, Philippines, Singapore, South Africa, Thailand and Eurasia. 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 an issued patent in Australia and 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 four issued or allowed patents in the United States, Europe, Canada and Australia, and one pending patent application in the United States. 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 UKII Limited and UCL Business, Plc (the "Second UCLB License Agreement"); and (iii) the license agreement, dated March 15, 2018, among MeiraGTx Limited, MeiraGTx UKII 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 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 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 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 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 the Stand-Alone Agreement related to CNGB3, we paid UCLB an upfront payment of £1.5 million and issued £1.5 million 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 £39.75 million in the aggregate and an annual management fee of £50,000 until certain royalty payments have been paid. Additionally, pursuant to the Stand-Alone UCLB Agreement related to CNGB3, we agreed to pay UCLB an upfront payment of £1.5 million and issue £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 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 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. Our policy requires 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 European Union and United States.

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 future 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. Before clinical testing of biological products in the United States may begin, we must submit an investigational new drug application, or IND, to the FDA, which reviews the clinical protocol, and the IND must become effective before clinical trials may begin.

Gene therapy products must be approved by the FDA before they may be legally marketed in the United States and by the appropriate foreign regulatory agencies before they may be legally marketed in foreign countries. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. The FDA has published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy clinical trials for delayed adverse events, potency testing, and chemistry, manufacturing and control information in gene therapy INDs.

To date, the FDA has approved three human gene therapy products for sale, including Kite Pharma's Yescarta, Novartis' Kymriah and Spark's Luxturna, and has provided general guidance regarding the development of gene therapy products. For example, the FDA has established the Office of Tissue and Advanced Therapies within 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 reviews. In addition, the FDA has issued a growing body of clinical guidelines, chemical, manufacturing and control, or CMC, guidelines and other guidelines, all of which are intended to facilitate industry's development of gene therapy products.

Ethical, social and legal concerns about gene-editing technology, gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any product candidates. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biological Products Development Process

The FDA determined that more than minimally manipulated 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, 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 application, 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. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate such trials. 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, had historically been subject to review by the Recombinant DNA Advisory Committee, or RAC, pursuant to the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. On August 17, 2018, the NIH issued a notice in the Federal Register and issued a public statement proposing changes to the oversight framework for gene therapy trials, including changes to the applicable NIH Guidelines to modify the roles and responsibilities of the RAC with respect to human clinical trials of gene therapy products, and requesting public comment on its proposed modifications. During the public comment period, which closed October 16, 2018, the NIH has announced that it will no longer accept new human gene transfer protocols for review as a part of the protocol registration process or convene the RAC to review individual clinical protocols. These trials will remain subject to the FDA's oversight and other clinical trial regulations, and oversight at the local level will continue as set forth in the NIH Guidelines. Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. 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. Clinical trials also must be reviewed by an IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

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 rare 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.

Human gene therapy products based on gene-editing technology are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these trials will be acceptable to the FDA to support marketing approval. The NIH and the FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene transfer trials and serves as an electronic tool to facilitate the reporting and analysis of adverse events in these trials.

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 PHS Act 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.

The Food and Drug Administration Safety and Innovation Act, or FDASIA, requires that 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 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. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

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 also is subject to 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. Under PDUFA, the FDA has agreed to certain performance goals to complete the review of BLAs. The FDA may give a priority review designation to biological products that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the current PDUFA agreement, these six and ten month review periods are measured from the "filing" date rather than the receipt date for original BLAs, which typically adds approximately two months to the timeline for review and decision from the date of submission.

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. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. 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 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.

Additionally, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could impact the timeline for regulatory approval or otherwise impact ongoing development programs. For example, in December 2016, the 21st Century Cures Act was signed into law. This act is intended, among other things, to modernize the regulation of drugs and biologics and to spur innovation, and contains provisions specific to the development of cell therapies.

One of the performance goals agreed to by the FDA under the PDUFA is to review 90% of standard BLAs in ten months from the filing date and 90% of priority BLAs in six months from the filing date, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

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 indication 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 the 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.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or 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. 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.

In addition, under the provisions of FDASIA, enacted in 2012, the FDA established a Breakthrough Therapy Designation which is intended to expedite the development and review of products that treat serious or life-threatening diseases or conditions. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug 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. The Breakthrough Therapy Designation is a distinct status from both accelerated approval and priority review, but these can also be granted to the same product candidate if the relevant criteria are met. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.

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 we receive one of these designations for our product candidates, the FDA may later decide that our product candidates no longer meets the conditions for qualification. In addition, receiving these designations may not provide us with a material commercial advantage.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to cGMP requirements. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products 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.

To help reduce the increased risk of the introduction of adventitious agents, the PHSA Act emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHSA Act also provides authority to the FDA to immediately suspend biologics licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases within the United States.

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. Any agency or judicial enforcement action could have a material adverse effect on us.

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.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under Hatch-Waxman Act. The Hatch-Waxman Act permit a patent restoration term of up to five years as compensation for patent term lost

during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. 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 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. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend 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 BLA.

For patents that might expire during the BLA review phase, the patent owner may request an interim patent term extension. If eligible, an interim patent term extension may be granted for a period of not more than one year. The patent owner may apply for not more than four subsequent interim extensions. Any interim extension granted will not be longer than the maximum period of extension allowed post-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. To date, only a handful of biosimilars have been licensed under the BPCIA, and numerous biosimilars have been approved in Europe. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

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. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

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.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. In addition, recent government proposals have sought to reduce the 12-year reference product exclusivity period. Other

aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation, and meaning of the BPCIA remains subject to significant uncertainty.

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. Such laws include, without limitation: the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, to induce, or in return for, either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under any federal healthcare program; federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to the federal government, including federal healthcare programs, that are false or fraudulent; the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes which prohibit, among other things, executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters; HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their implementing regulations, which imposes certain requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information; the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to annually report to the federal government, information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and state and foreign law equivalents of each of the above federal laws, which, in some cases, differ from each other in significant ways, and may not have the same effect, thus complicating compliance efforts. 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, civil and criminal penalties, damages, fines, 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 individual 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 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 contains 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, and we expect there will be additional challenges and amendments to the ACA in the future. For example, the Tax Cuts and Jobs Act of 2017 was enacted, which, among other things, removes penalties for not complying with ACA's individual mandate to carry health insurance. On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. While the Texas U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the law.There is still uncertainty with respect to the impact President Trump's administration and the U.S. Congress may have, if any, and any changes will likely take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by 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 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 federal level,CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. On January 31, 2019, the HHS Office of Inspector General proposed modifications to U.S. federal Anti-Kickback Statute safe harbors which, among other things, will affect rebates paid by manufacturers to Medicare Part D plans, the purpose of which is to further reduce the cost of drug products to consumers. Although some of these, and other proposals will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs 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. 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 will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials 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.

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. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical trial development may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. 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.

Clinical Trials

Clinical trials of medicinal products in the European Union must be conducted in accordance with European Union and national regulations and the International Conference on Harmonization, or ICH, guidelines on GCPs. Additional GCP guidelines from the European Commission, focusing in particular on traceability, apply to clinical trials of advanced therapy medicinal products. If the sponsor of the clinical trial is not established within the European Union, it must appoint an entity within the European Union to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU countries, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization from the competent authority, and a positive opinion from an independent ethics committee. The application for a clinical trial authorization 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. Currently, clinical trial authorization applications must be submitted to the competent authority in each EU Member State in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is currently expected to take effect in 2019, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the clinical trial applications must be notified to or approved by the relevant competent authorities and ethics committees. Medicines used in clinical trials must be manufactured in accordance with cGMP. Other national and European Union-wide regulatory requirements also apply.

During the development of a medicinal product, the EMA and national medicines regulators within the European Union 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

To obtain regulatory approval of an investigational biological product under EU regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements. The process for doing this depends, among other things, on the nature of the medicinal product.

The centralized procedure results in a single marketing authorization, or MA, granted by the European Commission that is valid across the EEA (i.e., the European Union as well as Iceland, Liechtenstein and Norway). The centralized procedure is compulsory for human drugs that are: (i) derived from biotechnology processes, such as genetic engineering, (ii) contain 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) officially designated orphan medicines and (iv) advanced-therapy medicines, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The centralized procedure may at the request of the applicant also be used in certain other cases. Therefore, the centralized procedure would be mandatory for the products we are developing.

The Committee for Advanced Therapies, or CAT, is responsible in conjunction with the CHMP for the evaluation of 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 a marketing authorization application 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 a marketing authorization application; 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 in the European Union, 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 is opinion favorable, the Commission may then adopt a decision to grant an MA. In exceptional cases, the CHMP might perform an accelerated review of an MAA in no more than 150 days (not including clock stops). This is usually when the product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation.

The European Commission may grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations 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 marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations 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 timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

The European Commission may also grant a so-called "marketing authorization under exceptional circumstances". Such authorization 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, 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, marketing authorization 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.

A marketing authorization 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 marketing authorization being suspended or revoked. The renewal of a marketing authorization of a medicinal product under exceptional

circumstances, however, follows the same rules as a "normal" marketing authorization. Thus, a marketing authorization 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. A marketing authorization under exceptional circumstances should not be granted when a conditional marketing authorization is more appropriate.

The European Union 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 European Union also provides opportunities for market exclusivity. Marketing authorization applications for generic medicinal products do not need to include the results of preclinical and clinical trials, but instead can refer to the data included in the marketing authorization of a reference product for which regulatory data exclusivity has expired. In the European Union, upon receiving marketing authorization, new chemical entities generally receive eight years of data exclusivity and an additional two years of market exclusivity. The two-year period may be extended to three years if during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the EU regulatory authorities to be a new chemical 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 European Union. 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

Products receiving orphan designation in the European Union can receive ten years of market exclusivity. During the ten-year market exclusivity period, the EMA cannot accept another application for a marketing authorization, or grant a marketing authorization or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, 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

European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers. 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 marketing authorization is submitted. 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. Additionally, an MA may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- the applicant consents to a second orphan medicinal product application; or
- the applicant cannot supply enough orphan medicinal product.

Pediatric Investigation Plan

In the EMA, MAAs for new medicinal products not authorized have to include the results of trials conducted in the pediatric population, in compliance with a pediatric investigation plan, or 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 trial results are included in the product information, even when negative, the product is eligible for a six-months supplementary protection certificate extension.

Post-Approval Controls

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 marketing authorization. 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. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

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 European Union. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each EU Member State and can differ from one country to another.

Pricing and Reimbursement

Governments influence the price of medicinal products in the European Union 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. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. 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.

PRIME Scheme

In July 2016 the EMA launched PRIME scheme. 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 however not guaranteed. The benefits of a PRIME designation includes the appointment of a rapporteur from the CHMP before submission of an MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review earlier in the application process.

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 in: (i) response to an unsolicited order from a healthcare professional responsible for the care of the patient, (ii) 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) the product is manufactured under a specials license granted by the UK's MHRA.

Manufacturing a special also imposes a five year record retention requirements 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 covering data privacy and the protection of health-related and other personal information. EU member states and other jurisdictions have adopted data protection laws and regulations, which impose significant compliance obligations. Laws and regulations in these jurisdictions apply broadly to the collection, use, storage, disclosure, processing and security of personal information that identifies or may be used to identify an individual, such as names, contact information, and sensitive personal data such as health data. These laws and regulations are subject to frequent revisions and differing interpretations, and have generally become more stringent over time.

The General Data Protection Regulation, or GDPR, is a European framework law which imposes many requirements for controllers and processors of personal data, including, for example, higher standards for obtaining consent from individuals, if this is required, to process their personal data, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention and secondary use of personal data, increased requirements pertaining to health data and pseudonymised (i.e., key-coded) data and additional obligations when we contract third-party processors in connection with the processing of t personal data. The GDPR allows EU member states to make additional laws and regulations further limiting 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 €20,000,000 or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, and other administrative penalties.

The United Kingdom is expected to leave the European Union on March 29, 2019 further to the "Brexit" referendum. The UK's Data Protection Act 2018, or DPA2018, governs the UK's privacy regime and will continue to do so after the United Kingdom exits the EU. The DPA2018 incorporates the GDPR's text in full, with only minor amendments and further derogations including those pertaining to the processing of health data. Accordingly, the terms of the GDPR, and its significant penalties, will continue to apply after the UK exits the EU. At time of writing, it is still unclear whether the UK will be granted adequacy by the European Commission. In any event, for, at least, an interim period, export mechanisms, such as Model Clauses, will likely need to be put in place to govern the transfer of personal data from the EU to the UK.

Employees

As of December 31, 2018, we had 68 employees, all of which are full-time employees and 12 of which have M.D. or Ph.D. degrees. Of these full-time employees, 54 are engaged in research and development activities. 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.

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 IPO, we reorganized whereby MeiraGTx Limited became a wholly owned subsidiary of MeiraGTx Holdings plc.

Available Information

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 under the Investors and Media section of our website at *www.meiragtx.com*. Our website and the information contained on or connected to that site are not incorporated into this Form 10-K.

ITEM 1A. RISK FACTORS

You should carefully consider the risks and uncertainties described below and the other information in this Form 10-K before making an investment in our ordinary shares. Our business, financial condition, results of operations or prospects could be adversely affected if any of these risks occurs, and as a result, the market price of our ordinary shares could decline and you could lose all or part of your investment. This Form 10-K also contains forward-looking statements that involve risks and uncertainties. See "Special Note Regarding Forward-Looking Statements." Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including those set forth below.

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 $82.9 million and $31.0 million for the years ended December 31, 2018 and December 31, 2017, respectively. As of December 31, 2018, we had an accumulated deficit of approximately $148.3 million. Since our inception, we have devoted substantially all of our resources to developing our technology platform, establishing our viral vector manufacturing 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, business planning, raising capital, and providing general and administrative support for these operations. We have not yet demonstrated an ability to successfully complete a clinical program, including 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. Typically, it takes about six to ten years to develop a new drug from the time it enters Phase 1 clinical trials to when it is approved for treating patients, but in many cases it may take longer. Consequently, 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 and development activities, develop new product candidates, 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. 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 when, or if, we will be able to begin generating revenue from the commercialization of products or achieve or maintain profitability. Our expenses will also increase substantially as we operate as a public company and add clinical, scientific, operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as to support our transition to a public reporting company.

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 U.S. Food and Drug Administration, or FDA, European Medicines Agency, or 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 and negative cash flows for the foreseeable future. These net losses and negative cash flows 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. We 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 to enable us to complete the development and potential commercialization of our product candidates. 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 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.

Our operations have consumed significant amounts of cash since inception. As of December 31, 2018, our cash and cash equivalents were $68.1 million. Additionally, during the period from January 1, 2019 through the date of this filing, we have received additional funds in the aggregate amount of approximately $77.4 million and expect to receive an additional $100 million pursuant to the terms of the Collaboration Agreement. Therefore, based on our cash and cash equivalents after receiving the additional $177.4 million, we estimate that such funds will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into 2022. 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 consume capital significantly faster than we currently anticipate, and we may need to spend more than currently expected because of circumstances beyond our control. Because the length of time and activities associated with successful development of our product candidates is highly 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 *CNGB3* gene therapy product candidate, AAV-CNGB3, for our *RPE65*-deficiency product candidate, AAV-RPE65, for our X-linked retinitis pigmentosa product candidate, AAV-RPGR, for our radiation induced xerostomia and Sjogren's syndrome-associated xerostomia or xerophthalmia product candidate, AAV-AQP1, and continue to conduct our ongoing natural history studies for inherited retinal diseases, or IRDs;
- the initiation of Phase 1/2 clinical trials for our *CNGA3* gene therapy product candidate, AAV-CNGA3, and for our product candidate for the treatment of xerostomia associated with Sjogren's syndrome, AAV-AQP1;

- future discussions with regulatory agencies and potential subsequent initiation of future clinical trials for our product candidate for the treatment of Parkinson's disease, AAV-GAD;
- continuing our current research programs, our preclinical development of product candidates from our current research programs and further developing our gene regulation technology;
- 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;
- establishing a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA, 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 facility and processes;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the cost of making royalty, milestone or other payments under current and any future in-license agreements;
- the extent to which we in-license or acquire other products 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.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or potentially discontinue operations.

To the extent that we raise additional capital through the sale of equity or convertible debt 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 common shareholder. Debt financing and preferred equity 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. 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 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.

To date, we have invested a significant portion of our efforts and financial resources in the development of AAV-CNGB3, AAV-CNGA3, AAV-RPGR, AAV-RPE65 and AAV-AQP1. 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 these product candidates. We currently have no products that are approved for commercial sale and may never be able to develop marketable products. We expect to invest a meaningful portion of our efforts and expenditures over the next few years in AAV-GAD, AAV-CNGB3, AAV-CNGA3, AAV-RPGR, AAV-RPE65 and AAV-AQP1 (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. Accordingly, our business currently depends heavily on the successful development, regulatory approval and commercialization of our Most Advanced Product Candidates, which may never occur. 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, EMA or other regulatory bodies, we cannot be certain that our product candidate will be successfully commercialized, 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, EMA 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 European Union until we receive approval for a Marketing Authorization Application, or MAA, from the EMA, and we cannot market them in other countries until we receive any other required regulatory approval in those countries.

AAV-GAD, AAV-CNGB3, AAV-CNGA3, AAV-RPGR, AAV-RPE65 and AAV-AQP1 are our most advanced product candidates, and because some of our other product candidates are based on similar technology, if our Most Advanced 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.

To date, we have not had any formal meetings with regulatory agencies nor determined the regulatory pathway and any potential related development costs for our recently acquired AAV-GAD gene therapy program for Parkinson's disease.

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

We intend to identify and develop product candidates based on our novel gene therapy platform, which makes it difficult to predict the time and cost of product candidate development. Very few products that utilize transduction technology have been approved in the United States or in Europe, and there have only been a limited number of clinical trials involving a gene therapy product candidate.

We have concentrated a portion of our research and development efforts on our gene therapy platform, which uses both transduction and gene regulation 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. There have been a limited number of clinical trials of gene transduction technologies, with only one product candidate ever approved by the FDA.

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 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, recent 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. We may also experience delays and challenges in utilizing our manufacturing facility and achieving sustainable, reproducible, and scalable production. 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. Also, animal models may not exist for some of the diseases we expect to pursue.

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 EMA and FDA. 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. 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, a local institutional committee that reviews and oversees basic and clinical research conducted at the institution participating in the clinical trial. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the United States National Institutes of Health, or the NIH, had historically been subject to review by the NIH Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules, or NIH Guidelines. Following an initial review, RAC members would make a recommendation as to whether the protocol raised important scientific, safety, medical, ethical or social issues that warranted in-depth discussion at the RAC's quarterly meetings. Although the FDA decides whether individual gene therapy protocols may proceed under an IND, the RAC's recommendations were shared with the FDA and the RAC public review process, if undertaken, could have impeded or delayed the initiation of a clinical trial, even if the FDA had reviewed the trial and approved its initiation or had notified the sponsor that the study may begin. Conversely, the FDA can put an IND on clinical hold even if the RAC provided a favorable review or has recommended against an in-depth, public review.

On August 17, 2018, the NIH issued a notice in the Federal Register and issued a public statement proposing changes to the oversight framework for gene therapy trials, including changes to the applicable NIH Guidelines to modify the roles and responsibilities of the RAC with respect to human clinical trials of gene therapy products, and requesting public comment on its proposed modifications. During the public comment period, which closed on October 16, 2018, the NIH has announced that it will no longer accept new human gene transfer protocols for review as part of the protocol registration process under the existing NIH Guidelines or convene the RAC to review individual clinical protocols. These trials will remain subject to the FDA's oversight and other clinical trial regulations, and oversight at the local level will continue as otherwise set forth in the NIH Guidelines. Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC. 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. Even though we may not be required to submit a protocol for our gene therapy product candidates through the NIH for RAC review, we will still be subject to significant regulatory oversight by the FDA, and in addition to the government regulators, the applicable IBC and institutional review board, or IRB, of each institution at which we or our collaborators conduct clinical trials of our product candidates, or a central IRB if appropriate, would need to review and approve the proposed clinical trial.

In Europe, the EMA's Committee for Advanced Therapies, or CAT, is responsible for assessing the quality, safety, and efficacy of advanced-therapy medicinal products. Advanced-therapy medicinal products 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 European Union, 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.

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, the EMA, 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, the EMA, 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, the 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, 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 and 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 or foreign 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 or foreign regulatory authorities for support of a marketing application, 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 trials required for the approval of our product candidates. Although we have already begun Phase 1/2 clinical trials, we may experience delays in conducting any clinical trials and we do not know whether our clinical trials will begin on time, need to be redesigned, 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, EMA or other regulatory authorities as to the design or implementation of our clinical trials;
- obtaining regulatory approval to commence a clinical trial;
- reaching an agreement on acceptable terms with clinical trial sites or prospective CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- obtaining institutional review board, or IRB, approval at each site;
- recruiting suitable patients to participate in a clinical trial;
- developing and validating the companion diagnostic to be used in a clinical trial, if applicable;
- having patients complete a clinical trial or return for post-treatment follow-up;
- clinical sites, contract research organizations, 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;
- adding a sufficient number of clinical trial sites; or
- manufacturing sufficient quantities of product candidate 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;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate; and
- any future collaborators that conduct clinical trials may face any of the above issues, and 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, EMA or other 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, EMA 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. For example, our IND for AAV-RPE65 was filed in July 2017. On August 16, 2017, we received notification from the FDA supporting the use of the described batches of product candidate in the Phase 1/2 clinical trial. However, we received a recommendation from the FDA on a certain aspect of the manufacturing process for future clinical trials, thus putting our IND for AAV-RPE65 on partial clinical hold. We responded to the FDA on October 2, 2017 and, based on this response, the partial clinical hold was lifted on October 17, 2017. As another example, our IND for AAV-CNGB3 was filed on October 31, 2017. We received a question from the FDA around our injection device compatibility assay, thus putting our AAV-CNGB3 IND on clinical hold. In the device compatibility assay, the FDA noted a disparity between the target titer for the intended low dose dilution and the actual titer obtained on polymerase chain reaction, or PCR, analysis. The FDA requested clarification on whether this was an imprecise dilution scheme for the low dose or a PCR assay issue. We submitted our second response to the FDA on May 2, 2018 providing data that identified the issue as a PCR assay artifact and also showing data that we believe supports that this has now been addressed. On May 31, 2018, the FDA released the clinical hold on our IND for AAV-CNGB3.

Our most advanced product candidates, AAV-GAD, AAV-CNGB3, AAV-CNGA3, AAV-RPGR, AAV-RPE65 and AAV-AQP1, 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, EMA or other regulatory authorities on our clinical development program, and the FDA, 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.

The affected populations for our other 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 this Form 10-K should be viewed with caution. Further, the data and statistical information included, or supporting the information, in this Form 10-K, 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 European Union 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. Adverse 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, 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.

Even though we have been granted access to the PRIME scheme by the EMA for AAV-CNGB3 and the FDA granted Fast Track designation to AAV-RPGR and AAV-CNGB3, in the future we may seek and fail to obtain access to the PRIME scheme by the EMA or Fast Track designation by the FDA for other of our current or potential future product candidates. We may also seek and fail to obtain breakthrough therapy designation from the FDA for our current or any future product candidates. Such designations or access may also not lead to faster development or regulatory review or approval, and it does 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 FDA's review and approval of new drugs and biological products that meet certain criteria. For example, the FDA has a Fast Track 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, or if the drug has been designated as a qualified infectious disease product. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. Under Fast Track, 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, AAV-RPGR was designated a Fast Track program by the FDA for the treatment of X-linked retinitis pigmentosa owing to defects in RPGR. In August 2018, AAV-CNGB3 was designated a Fast Track program by the FDA for the treatment of achromatopsia caused by *CNGB3* mutations to improve visual function.

In 2012, the Food and Drug Administration Safety and Innovation Act, or FDASIA, established the breakthrough therapy designation. A sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the product candidate 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 candidate may demonstrate substantial improvement over existing therapies on one or more clinically-significant endpoints, such as substantial treatment effects observed early in clinical development. Sponsors may request that FDA designate a product candidate as a breakthrough therapy at the time of or any time after the submission of an IND, but ideally before an end-of-phase 2 meeting with FDA. If the FDA grants breakthrough therapy designation, it may take actions appropriate to expedite the development and review of the product candidate, which may include but are not limited to holding meetings with the sponsor and the review team throughout the development of the therapy; providing timely advice to, and interactive communication with, the sponsor regarding the development of the product candidate to ensure collection of appropriate data needed to support approval; more frequent written correspondence from the FDA about such things as the design of the proposed clinical trials and use of biomarkers; intensive guidance on an efficient drug development program, beginning as early as Phase 1; organizational commitment involving senior managers; and eligibility for rolling review and priority review of a BLA. Breakthrough therapy designation comes with all of the benefits of Fast Track designation, which means that the sponsor may file sections of the BLA for review on a rolling basis if certain conditions are satisfied, including an agreement with FDA on the proposed schedule for submission of portions of the application and the payment of applicable user fees before the FDA may initiate a review. Fast Track designation, priority review and breakthrough therapy designation do not change the standards for approval but may expedite the development or approval process.

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.

Fast Track designation and designation as a breakthrough therapy are within the discretion of the FDA. Accordingly, even if we believe one of our other product candidates meets the criteria for Fast Track designation

or designation as a breakthrough therapy and we seek such designation, the FDA 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 Fast Track designation or breakthrough therapy designation will meet the FDA's expectations. In any event, the receipt of a Fast Track designation or breakthrough therapy designation for a product candidate may not result in a faster development process, review, or approval compared to product candidates considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if additional product candidates are granted Fast Track designation or one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Similarly, access to the PRIME scheme is at the discretion of the EMA, and we cannot be sure that any additional current or future product candidates will be granted access to the scheme; that participation in the scheme will result in expedited regulatory review or approval of our product candidates; or that access to the scheme, once granted, will not be revoked.

We have received orphan drug designation from the FDA and EMA for AAV-CNGB3, AAV-CNGA3, AAV-RPE65, AAV-RPGR, AAV-AIPL1 and FDA for AAV-AQP1 and 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 European Union, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating, or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product or where there is no satisfactory method of diagnosis, prevention, or treatment, or, if such a method exists, the medicine must 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 indication 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 active ingredient for the same indication, unless the drug is demonstrated to be clinically superior to the previously approved drug. In the European Union, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following approval for the approved therapeutic indication. This period may be reduced to six years if, at the end of the fifth year, the orphan drug designation criteria are no longer met, including where it is shown that the drug is sufficiently profitable not to justify maintenance of market exclusivity. In the European Union, a marketing authorization for an orphan designated product will not be granted if a similar drug has been approved in the European Union for the same therapeutic indication, unless the applicant can establish that its product is safer, more effective or otherwise clinically superior. A similar drug 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.

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, AAV-RPE65 for the treatment of Leber congenital amaurosis, AAV-RPGR for the treatment of retinitis pigmentosa and AAV-AIPL1 for the treatment of inherited retina dystrophy due to defects in *AIPL1* gene, and we obtained orphan drug designation from the FDA for AAV-CNGA3 for the treatment of achromatopsia due to autosomal-recessive *CNGA3* gene mutations and for AAV-AQP1 for the treatment of grade 2 and grade 3 late xerostomia from parotid gland hypofunction caused by radiotherapy, and we obtained orphan medicinal product designation from the EMA for AAV-CNGA3 for the treatment of achromatopsia. We plan to 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 may be unavailable if we seek approval for an indication broader than the orphan-designated indication or may be lost in the United States if the FDA later determines 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 drugs with different active moieties can be approved for the same condition. In addition, the FDA and the EMA can subsequently approve products with the same active moiety for the same condition if the FDA or the EMA concludes that the later drug is safer, more effective, or makes a major contribution to patient care. 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. In 2014, a U.S. district court invalidated the FDA's denial of orphan exclusivity to an orphan designated drug, which the FDA had based on its determination that the drug was not proven to be clinically superior to a previously approved "same drug." In response to the decision, the FDA released a policy statement stating that the court's decision is limited to the facts of that particular case and that the FDA will continue to deny orphan drug exclusivity to a designated drug upon approval if the drug is the "same" as a previously approved drug, unless the drug is demonstrated to be clinically superior to that previously approved drug. Since then, similar legal challenges have been initiated against the FDA for its denial of orphan drug exclusivity to other designated drugs, and in 2017, Congress amended the Orphan Drug Act to require a demonstration of clinical superiority upon approval as a condition of receiving orphan drug exclusivity when another "same drug" has already been approved for the same indication. In the future, there is the potential for additional legal challenges to the FDA's orphan drug regulations and policies, and it is uncertain how ongoing and future challenges might affect our business.

We and our contract manufacturer for plasmid are subject to significant regulation with respect to manufacturing our products. Our manufacturing facilities and the third-party manufacturing facility 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 cGMP manufacturing facility in early 2018. However, if we experience slowdowns or problems with our facility 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 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 in the European Union 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 approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. 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 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 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. A material shortage, contamination, recall or restriction on the use of biologically derived substances in

the manufacture of our product candidates 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.

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

In addition, our clinical trials may compete with 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, and this competition may reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors, or chose to be treated using Luxturna, a commercially available product by Spark Therapeutics, Inc. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which may reduce the number of patients who are available for our clinical trials in such clinical trial site.

Delays or failures in planned patient enrollment or retention 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.

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, EMA 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 oncogenesis.

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, EMA or CAT could suspend or terminate our clinical trials or the FDA, EMA 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;
- 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. Many companies in the pharmaceutical and

biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

The regulatory approval processes of the FDA, EMA 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, EMA 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. 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 or the European Union until we receive regulatory approval of a BLA from the FDA or a MAA from the EMA, respectively. It is possible that the FDA may refuse to accept for substantive review any biologic license applications, or BLAs, or the 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 European Union or elsewhere, we or our collaborators must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the FDA, 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, EMA or other regulatory authorities. The FDA 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 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, EMA 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 Agreement partner obtain FDA or EMA approval for AAV-GAD, AAV-CNGB3, AAV-CNGA3, AAV-RPGR, AAV-RPE65 or AAV-AQP1 in the United States or European Union, we may never obtain approval for or commercialize it 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 or the EMA in the European Union 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 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, EMA 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 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 and EMA 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 and EMA imposes 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.

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 third-party manufacturers or manufacturing processes, 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 policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and biologics and spur innovation and contains provisions applicable to the development of gene therapies, but its ultimate implementation is unclear. 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.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, the Trump administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Interim "top-line" 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 publish interim "top-line" or preliminary data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or "top-line" data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects.

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.

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 European Union 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, and we expect there will be additional challenges and amendments to the ACA in the future. For example, the Tax Cuts and Jobs Act of 2017 was enacted, which includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additionally, on December 14, 2018, a U.S. District Court Judge in Texas ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act, or the Tax Act. While such U.S. District Court Judge, as well as the Trump administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the law. The current Trump administration and Congress will likely continue to seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. It is uncertain the extent to which any such changes may impact our business or financial condition.

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 2027 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. The Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. On January 31, 2019, the HHS Office of Inspector General proposed modifications to U.S. federal Anti-Kickback Statute safe harbors which, among other things, will affect rebates paid by manufacturers to Medicare Part D plan sponsors, Medicaid managed care organizations, and those entities' pharmacy benefit managers ("PBMs"), the purpose of which is to further reduce the cost of drug products to consumers. Although some of these, and other, proposals will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. 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.

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.

In the European Union, 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 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

European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than European Union, 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 most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing European Union and 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 and the European Union, 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 European Union 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 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 prohibit, among other things,, including through civil whistleblower or qui tam actions, individuals or entities from 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;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and its implementing regulations, which imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without appropriate authorization by covered entities subject to the rule, such as certain health plans, healthcare clearinghouses and healthcare providers as well as their business associates, independent contractors of a covered entity that perform certain services involving the use or disclosure of individually identifiable health information;
- 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 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; state and local laws that require the registration of pharmaceutical sales representatives; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts; and
- similar healthcare laws and regulations in the European Union and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and requirements regarding the collection, distribution, use, security, and storage of personally identifiable information and other data relating to individuals (including the EU General Data Protection Regulation 2016/679, or GDPR.

As of May 25, 2018, the GDPR replaced the Data Protection Directive with respect to the processing of personal data in the European Union. The GDPR imposes many requirements for controllers and processors of personal data, including, for example, higher standards for obtaining consent from individuals to process their personal data, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention and secondary use of information, increased

requirements pertaining to health data and pseudonymised (i.e., key-coded) data and additional obligations when we contract third-party processors in connection with the processing of the personal data. The GDPR allows EU member states to make additional laws and regulations further limiting 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 €20,000,000 or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, and other administrative penalties.

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 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.

As with other companies engaged in activities similar to ours, we face a risk of 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, the production efforts of our third-party manufacturers or our development efforts 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 U.K. 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 United Kingdom and the United States, 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 U.K., 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 will seek to build and continuously improve our systems of internal controls 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, significant competition, and a strong emphasis on intellectual property. We will 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.

Our platform and products focus on the development of gene therapies and gene regulation technology. There are a number of companies developing ocular gene therapy products, including Applied Genetic Technologies Corporation, Nightstar Therapeutics plc and Spark Therapeutics, Inc. There are a number of companies developing gene therapy products for neurodegenerative diseases, including Voyager Therapeutics, Inc. and Axovant Sciences Ltd. 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, protein or other 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. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for 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 or that would render any products that we may develop obsolete or non-competitive. Our competitors also may obtain FDA, EMA 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. Additionally, technologies developed by our competitors may render our potential product candidates uneconomic or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

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 availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

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 once approved. Assuming there is coverage for our product candidates or procedures using our product candidates 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 European Union 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, and we believe that changes in these rules and regulations are likely.

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 products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- 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;
- 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, 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 this product 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. We expect to build a focused sales, distribution and marketing infrastructure to market our product candidates in the United States and European Union, if approved. 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 our internal sales, marketing and distribution capabilities could delay any product launch, which would adversely impact the commercialization of our product candidates. Additionally, if the commercial launch of our product candidates for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

We may not have the resources in the foreseeable future to allocate to the sales and marketing of our product candidates in certain international 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-AQP1 or other future gene therapy programs, if approved, for the United States and/or certain markets overseas; however, we cannot assure 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 a collaborative relationship for the commercialization of AAV-GAD, AAV-RPE65 or AAV-AQP1, we may be forced to delay the potential

commercialization of AAV-GAD, AAV-RPE65 or AAV-AQP1 or reduce the scope of our sales or marketing activities for AAV-GAD, AAV-RPE65 or AAV-AQP1. 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 to AAV-GAD, AAV-RPE65 or AAV-AQP1 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 of 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 are unable to establish adequate sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing AAV-GAD, AAV-RPE65 or AAV-AQP1 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 we obtain approval to commercialize any products outside of the United States or the European Union, a variety of risks associated with international operations could adversely affect our business.

If AAV-GAD, AAV-RPE65 or AAV-AQP1 are approved for commercialization, we intend to enter into agreements with third parties to market them in certain jurisdictions outside the United States and the European Union. We expect that we 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;
- reduced 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 natural disasters including earthquakes, typhoons, floods and fires, or from economic or political instability;
- greater difficulty with enforcing our contracts;
- potential noncompliance with the U.S. Foreign Corrupt Practices Act, the U.K. Bribery Act 2010 and similar anti-bribery and anticorruption laws in other jurisdictions; and
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad.

We have no prior experience in these areas. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by individual countries in Europe with which we 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. 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 their product. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have an adverse effect on the future commercial prospects for our biological products.

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. Moreover, the extent to which a biosimilar, once approved, 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.

Risks Related to Our Dependence on Third Parties

If our cGMP manufacturing facility is 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 facility. However, if our facility is damaged, suffers any form of delay or regulatory challenges, 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.

We currently rely on third-party manufacturers for the manufacture of plasmid used in the production 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 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;
- 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.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements that might be required by the FDA 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 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 may collaborate with third parties for the development 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 may seek collaborative relationships for the development and commercialization of our product candidates. 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. Moreover, any collaborative partners we enter into agreements with in the future may shift their priorities and resources away from our product candidates or seek to renegotiate or terminate their relationships with us.

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 UCL Business, Plc, or UCLB, and Brandeis University, or Brandeis, and the National Institute of Dental and Craniofacial Research, or NIDCR, a division of the NIH. We are a party to agreements with UCLB for certain technology and AAV vector-related patents and with Brandeis for certain preclinical technology for the treatment of ALS. Further, we are party to an agreement with NIDCR for technology relating to the treatment of Sjogren's syndrome. We may 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. For example, in exchange for the rights granted to us by UCLB, we are obligated to pay an annual management fee, milestone payments for certain commercial sales thresholds, and a certain percentages of proceeds on sublicensing revenues. If we fail to comply with our obligations to UCLB, Brandeis, NIDCR, or any of our other 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 proceeding 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.

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 large 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 highly uncertain.

It is also possible that we will 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 foreign 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. 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 highly 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. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. 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. Since patent applications in the United States and other jurisdictions are confidential for a period of time after filing, we cannot be certain that we were the first to file for patents covering our inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in the issuance of patents, or may result in the issuance of patents which fail to protect our technology or products, in whole or in part, or which fail to effectively prevent others from commercializing competitive technologies and products.

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. The various markets in which we plan to operate are subject to frequent and extensive litigation regarding patents and other intellectual property rights. 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. There may be third-party patents or patent applications with claims to compositions, formulations, or methods of treatment, prevention use, or manufacture of our product candidates or technologies. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover aspects of our compositions, formulations, or methods of treatment, prevention or use, 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 successful, 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. In addition, if the breadth or strength of protection provided the patents and patent applications we own or in-license is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

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. In patent litigation in the United States and in Europe, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness lack of written description, or non-enablement. Third parties might allege unenforceability of our patents because during prosecution of the patent an individual connected with such prosecution withheld relevant information, or made a misleading statement. Interference or derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications. The outcome of proceedings involving assertions of invalidity and

unenforceability during patent litigation is unpredictable. With respect to the validity of patents, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution, but that an adverse third party may identify and submit in support of such assertions of invalidity. 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. Our patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without infringing our patents or other intellectual property rights.

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. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors view these announcements in a negative light, the price of our ordinary shares could be adversely affected. 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, Europe 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 European Union 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 European Union 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.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology and genetic medicine industries involve both technological complexity and legal complexity. Therefore, obtaining and enforcing biotechnology and genetic medicine patents is costly, time-consuming and inherently uncertain. 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 going forward 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.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. 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, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action.

Accordingly, 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. It is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors' patent applications and the enforcement or defense of our or our licensors' issued patents.

We may become involved in opposition, interference, derivation, inter partes review or other proceedings challenging our or our licensors' patent rights, and the outcome of any proceedings are highly uncertain. 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 in the future that may be important for our business.

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.

The USPTO, European and other patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO, European and other patent agencies over the lifetime of a patent. While an inadvertent failure to make payment of such fees or to comply with such provisions can in many cases be cured by additional payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance with such provisions will result in the abandonment or lapse of the patent or patent application, and the partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents within prescribed time limits. If we or our licensors fail to maintain the patents and patent applications covering our product candidates or if we or our licensors otherwise allow our patents or patent applications to be abandoned or lapse, it can create opportunities for competitors to enter the market, which would hurt our competitive position and could impair our ability to successfully commercialize our product candidates in any indication for which they are approved.

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 or the European Union. 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.

In addition, we may decide to abandon national and regional patent applications while they are still pending. The grant proceeding of each national or regional patent is an independent proceeding which may lead to situations in which applications may be rejected by the relevant patent office, while substantively similar applications are granted by others. For example, relative to other countries, China has a heightened requirement for patentability and specifically requires a detailed description of medical uses of a claimed drug. Furthermore, generic drug manufacturers or other competitors may challenge the scope, validity or enforceability of our or our licensors' patents, requiring us or our licensors to engage in complex, lengthy and costly litigation or other proceedings. Generic drug manufacturers may develop, seek approval for and launch generic versions of our products. It is also quite common that depending on the country, the scope of patent protection may vary for the same product candidate or technology.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws or regulations in the United States and the European Union, 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 to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate, which may have an adverse effect on our ability to successfully commercialize our product candidates in all of our expected significant foreign markets. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished and we may face additional competition in those jurisdictions.

In some jurisdictions, compulsory licensing laws compel patent owners to grant licenses to third parties. In addition, some countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors are forced to grant a license to third parties under patents relevant to our business, or if we or our licensors are prevented from enforcing patent rights against third parties, our competitive position may be substantially impaired in such jurisdictions.

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 European Union, our product candidates may be eligible for term extensions based on similar legislation. In either jurisdiction, 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 in effect shortened and our competitors may obtain approval to market competing products sooner. The resulting reduction of years of 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;
- it is possible that our pending patent applications will not result in issued patents;
- it is possible that there are prior public disclosures that could invalidate our or our licensors' patents;
- 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;
- 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;
- ownership, validity or enforceability of our or our licensors' patents or patent applications may be challenged by third parties; and
- the patents of third parties or pending or future applications of third parties, if issued, may have an adverse effect on our business.

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. 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.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

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 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 additional intellectual property from third parties, and such licenses 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 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, 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.

We may 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.

We employ individuals who were previously employed at other biotechnology or pharmaceutical companies. Although we seek to protect our ownership of intellectual property rights by ensuring that our agreements with our employees, collaborators and other third parties with whom we do business include provisions requiring such parties to assign rights in inventions to us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Even if we are successful, litigation could result in substantial cost and reputational loss and be a distraction to our management and other employees.

Risks Related to Employee Matters and Managing Growth

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

As of December 31, 2018, we had 68 full-time employees. We will need to significantly expand our organization, and 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 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 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. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. 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 costs to defend the related litigation and related litigation;
- distraction of management's attention from our primary business;
- 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 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.

We also expect that continuing to operate as a public company will 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. We do not know, however, if we will be able 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) the laws and regulations of the FDA, EMA and other similar regulatory 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 would suffer in the event of system failures.

Our computer systems, as well as those of our contractors and consultants, are vulnerable to damage from computer viruses, unauthorized access, natural disasters (including hurricanes), terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product candidate development programs. 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. 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 collect 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, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or internal bad actors, or breached due to employee error, a technical vulnerability, malfeasance or other disruptions. Although, to our knowledge, we have not experienced any such material security breach to date, any such 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, and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay clinical development of our product candidates.

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

In the future, we may 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.

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

Following the vote of a majority of the eligible members of the electorate in the United Kingdom to withdraw from the European Union in a national referendum held on June 23, 2016, the U.K. government served notice under Article 50 of the Treaty of the European Union on March 29, 2017 to formally initiate a withdrawal process. The withdrawal agreement and political declaration that were endorsed at a special meeting of the European Council on November 25, 2018 did not receive the approval of the UK Parliament in January and March 2019. Further discussions are ongoing, although the European Commission has stated that the EU will not reopen the withdrawal agreement. The United Kingdom and the European Union have a two-year period under Article 50 to negotiate the terms for withdrawal. Any extension of the negotiation period for withdrawal will require the consent of all of the remaining 27 EU member states.

The referendum and anticipation of withdrawal have created significant uncertainty about the future relationship between the United Kingdom and the European Union. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which EU-derived laws and regulations to replace or replicate as part of a withdrawal, including healthcare and pharmaceutical regulations; financial laws and regulations; tax and free trade agreements; intellectual property rights; supply chain logistics; environmental, health, and safety laws and regulations; immigration laws; and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity, and restrict our access to capital. If the United Kingdom and the European Union are unable to negotiate mutually acceptable withdrawal terms or if other EU member states pursue withdrawal, barrier-free access between the U.K. and other EU member states or among the European economic area overall could be diminished or eliminated. These developments, or the perception that any of them could occur, have had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Asset valuations, currency exchange rates, and credit ratings may be especially subject to increased market volatility. In addition, changes to U.K. border and immigration policy could occur as a result of the United Kingdom's withdrawal from the European Union, affecting our ability to recruit and retain employees from outside the United Kingdom. Any of these factors could have an adverse effect on our business, financial condition, results of operations, and prospects.

Further, the vote for the United Kingdom's withdrawal from the European Union has resulted in a decision to move the EMA from the United Kingdom to the Netherlands, with operations currently scheduled to begin in the Netherlands by end of March 2019. This transition has caused, and may continue to cause, disruption in the administrative and medical scientific links between the EMA and the UK Medicines and Healthcare products Regulatory Agency, or the MHRA, including delays in granting clinical trial authorization or marketing

authorization, disruption of importation and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the European Union and/or the United Kingdom.

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

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 or recommendations by securities analysts;
- 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. 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, 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 the 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 control or significantly influence all matters submitted to shareholders for approval.

As of December 31, 2018, 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 approximately60.2% of our outstanding ordinary shares.

As a result, if these shareholders choose to act together, they would be able to control or 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 control or 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.

A significant portion of our total outstanding shares are eligible to be sold into the market, which could cause the market price of our ordinary shares to drop significantly, even if our business is doing well.

Sales of a substantial number of our ordinary shares in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our ordinary shares.

All lock-up agreements entered into in connection with our initial public offering expired on December 5, 2018. Subject to any applicable lockup agreement described below, our outstanding ordinary shares may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act, or to the extent that such shares have already been registered under the Securities Act and are held by non-affiliates of ours. Moreover, certain holders of ordinary shares have rights, subject to specified

conditions, to require us to file registration statements covering their shares or to include their ordinary shares in registration statements that we may file for ourselves or other shareholders, until such shares can otherwise be sold without restriction under Rule 144 or until the rights terminate pursuant to the terms of the shareholders agreement between us and such holders. We also have registered all ordinary shares that we may issue under our equity compensation plans or that are issuable upon exercise of outstanding options. Upon issuance, these ordinary shares can be freely sold in the public market, subject to volume limitations applicable to affiliates and any applicable lock-up agreements. Furthermore, we and our executive officers, directors and certain of our shareholders have agreed with the underwriters that, subject to certain exceptions, we and they will not directly or indirectly sell or otherwise transfer their ordinary shares for a period of 90 days after the completion of the offering.

Any sales of securities by these shareholders could have a negative impact on the trading 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 following the fifth 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:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure in this Form 10-K;
- 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 common 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 common

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, being required to provide only two years of audited financial statements and 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 shares price may be more volatile.

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

As a public company, and particularly after we are no longer an emerging growth company and smaller reporting company, we 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 and make some activities more time consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

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 within the prescribed period, we will be engaged 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 will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, 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.

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 as well as against the selling shareholders 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 jurisdictions courts against us or our directors or officers as well as against the selling shareholders 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 Law (2018 Revision), or the Companies Law, 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.

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

Section 404(a) of the Sarbanes-Oxley Act, or Section 404(a), requires that beginning with our second annual report following our IPO on June 7, 2018, management assess and report annually on the effectiveness of our internal control over financial reporting and identify any material weaknesses in our internal control over financial reporting. Although Section 404(b) of the Sarbanes-Oxley Act, or Section 404(b), requires our independent registered public accounting firm to issue an annual report that addresses the effectiveness of our internal control over financial reporting, we have opted to rely on the exemptions provided in the JOBS Act, and consequently will not be required to comply with SEC rules that implement Section 404(b) until such time as we are no longer an "emerging growth company."

We expect our first Section 404(a) assessment will take place for our annual report for the fiscal year ending December 31, 2019. Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, 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. Inadequate internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ordinary shares.

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. 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 additional information.

We could be subject to securities class action litigation.

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

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

Our board of directors conducts our affairs so that the central management and control of the company is exercised in the United Kingdom. As a result, we expect to be treated as resident in the United Kingdom 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 United Kingdom 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 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 composition of our income, assets and operations, we do not believe we were a "passive foreign investment company," or PFIC, for the taxable year ending on December 31, 2018, 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 ending on December 31, 2018 and 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. If we were to be classified as a PFIC for any taxable year during which a U.S. Holder (as defined below under "Material U.S. Federal Income Tax Consequences") holds our ordinary shares, certain adverse U.S. federal income tax consequences could apply to such U.S. Holder, including (i) the treatment of all or a portion of any gain on disposition of our ordinary shares as ordinary income, (ii) the application of a deferred interest charge on such gain and the receipt of certain dividends and (iii) the obligation to comply with certain reporting requirements.

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 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 should consult their tax advisors regarding the potential application of these rules to their investment in our ordinary shares.

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

The U.S. government has enacted comprehensive tax legislation that includes significant changes to the taxation of business entities, referenced herein as the Tax Reform Act. These changes include, among others, a permanent reduction to the corporate income tax rate, limiting interest deductions and the use of net operating losses, adopting elements of a territorial tax system and introducing certain anti-base erosion provisions. We continue to examine the impact this tax reform legislation may have on our business. The effect of the Tax Reform Act on our business, whether adverse or favorable, is uncertain, and may not become evident for some period of time. U.S. Holders should consult their legal and tax advisors regarding any such legislation and the potential tax consequences of investing 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. 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.

In October 2015, the Organization for Economic Co-Operation and Development released a final package of measures to be implemented by member nations in response to a 2013 action plan calling for a coordinated multi-jurisdictional approach to "base erosion and profit shifting" by multinational companies. Multiple member jurisdictions, including the countries in which we operate, have begun implementing recommended changes such as country-by-country reporting requirements and changes to double tax treaties. Additional multilateral changes are anticipated in upcoming years. We often rely on generally available interpretations of applicable tax laws, treaties and regulations. There cannot be certainty that the relevant tax authorities are in agreement with our interpretation of these laws, regulations or treaties, or with tax positions that we have taken. If our interpretation or tax position is challenged by the relevant tax authorities, we could be required to pay taxes that we currently do not collect or pay, may be subject to interest and penalties and there could be an increase to the costs of our services to track and collect such taxes, which could increase our costs of operations or our effective tax rate. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. The occurrence of any of the foregoing tax risks could have a material adverse effect on our business, financial condition and results of operations.

We are unable to predict what national or international tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could impact the tax treatment of our earnings, adversely affect our profitability and increase the complexity, burden and cost of tax compliance.

We have significant net operating losses, or NOLs, and U.K. carryforward tax losses which we may not be able to realize or which may be restricted following the Reorganization Transactions or any future change of control. We also benefit from certain tax incentive regimes, such as research and development tax credits, in the jurisdictions in which we operate and any adverse change to these regimes, the application thereof or challenges to the tax position we have adopted under these regimes could adversely affect our results of operations and financial condition.

As of December 31, 2018, we had federal and state NOL carryforwards in the United States of $14.2 million and $14.2 million, respectively, and cumulative carryforward tax losses in the United Kingdom of

$94.1 million, which we expect to be available to reduce future taxable income subject to any relevant restrictions (including those in the UK that limit the percentage of profits that can be reduced by carried forward losses). The U.S. federal and state NOL carryforwards incurred prior to January 1, 2018 in the amount of approximately $6.8 million and $6.7 million will begin to expire in 2036. The U.K. carryforward tax losses will continue indefinitely, subject to relevant restrictions, under current UK legislation. Under the Tax Cuts and Jobs Act of 2017, U.S. federal NOL carryforwards generated after December 31, 2017 are not subject to expiration but such NOLs may only offset 80% of taxable income. As of December 31, 2018, we also had orphan drug and research and development credits in the U.S. in the amount of $1.1 million.

The NOL carryforwards and U.K. carryforward tax losses are subject to review and possible adjustment by the U.S., U.K. and state tax authorities. NOL carryforwards and U.K. carryforward tax losses may become subject to limitations in the event of certain cumulative changes in the ownership interest of significant shareholders, as defined under Sections 382 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, 2018, there were no limitations in the U.K. However, for U.S. purposes, we have determined that a change of ownership occurred in April 2016. We are still in the process of determining the annual limitation on losses that occurred prior to April 2016. Subsequent ownership changes and changes to the UK (or US) tax rules in respect of the utilization of losses carried forward may further affect the limitation in future years.

Additionally, we have not undertaken a study on the completeness of the U.S. research and development and orphan drug credits. As such, the U.S. research and development and orphan drug credits may change and may be subject to review and adjustment by the tax authorities.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

Our principal office is located at 430 East 29th Street, 10th Floor, New York, New York 10016, USA, where we lease 5,887 square feet of office space. We lease this office space under a lease that terminates on December 31, 2021.

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 N1 7NQ, United Kingdom. The long leasehold interest is for 125 years, expiring in 2126, and there is no rent payable thereunder.

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 SECURITIES

Market Information

On June 8, 2018, our ordinary shares began trading on the Nasdaq Global Market under the symbol "MGTX." Prior to that time, there was no public market for our stock.

Holders of Record

As of March 15, 2019, there were 75 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. 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 March 1, 2019, we consummated a private placement with various investors, including one of our existing shareholders, Perceptive Life Sciences Master Fund Ltd., pursuant to which we issued and sold an aggregate of 5,797,102 of our ordinary shares at a purchase price of $13.80 per share. Evercore Group L.L.C. and Chardan Capital Markets LLC served as co-lead placement agents for the private placement and received an aggregate underwriting commission of approximately $2.4 million. The financing was led by Johnson & Johnson Innovation – JJDC, Inc. ("JJDC"), the investment arm of Johnson & Johnson, which made a $40.0 million equity investment in the Company and received 2,898,550 ordinary shares. Each of the foregoing securities issuances were in reliance on the exemption contained in Section 4(a)(2) of the Securities Act, as transactions by issuers not involving a public offering.

In connection with our amendment and restatement of our license agreements with UCLB whereby we agreed to issue UCLB £1.5 million of the Company's ordinary shares, on March 21, 2019, we issued 158,832 of the Company's ordinary shares to UCLB. This securities issuance was in reliance on the exemption contained in Section 4(a)(2) of the Securities Act, as a transaction by issuers not involving a public offering.

Use of Proceeds

On June 12, 2018, we completed our IPO and issued and sold 5,000,000 ordinary shares at a price to the public of $15.00 per share receiving $65.2 million in proceeds after deducting underwriting discounts and commissions and offering expenses payable by us. There has been no material change in the expected use of the net proceeds from our IPO as described in our prospectus. As of December 31, 2018, we had used $34.1 million of such net proceeds and had total unrestricted cash and cash equivalents of $68.1 million.

ITEM 6. SELECTED FINANCIAL DATA

Not applicable.

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 our financial statements and the related notes appearing at the end of this Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties. As a result of many factors, such as 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 may differ materially from those anticipated in these forward-looking statements. 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 five programs in clinical development and a broad pipeline of preclinical and research programs. We have core capabilities in viral vector design and optimization, gene therapy manufacturing as well as a potentially transformative gene regulation technology. 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. Though initially focusing on the eye, salivary gland and central nervous system, 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. Since our formation, we have devoted substantially all of our resources to developing our technology platform, establishing our viral vector manufacturing 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, business planning, raising capital, and providing general and administrative support for these operations. In 2016, we completed the acquisition of assets held by BRI-Alzan, Inc., a Delaware corporation, including a worldwide license agreement to develop certain preclinical technology for the treatment of ALS. In October 2018, we acquired Vector Neurosciences, Inc., a Delaware corporation. In connection with that acquisition, we acquired its AAV-GAD gene therapy program which had completed a randomized, sham-controlled Phase 2 study for treatment of Parkinson's disease. 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, 2018, we received gross proceeds of approximately $203.7 million from sales of our ordinary shares, Series A ordinary shares and Convertible Preferred C Shares. As of December 31, 2018, we had cash and cash equivalents of $68.1million.

We are a clinical stage company and have not generated any product revenues to date. We have five 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, 2018 and 2017 were $82.9 million and $31.1 million, respectively. As of December 31, 2018, we had an accumulated deficit of $148.3 million. While we do not expect to generate revenue from sales of any products for several years, if at all, in January 2019, we entered into the Collaboration Agreement, which provides for Janssen to pay us an $100 million upfront payment and provide us with research funding, and we are eligible to receive potential milestone payments and royalties.

Our total operating expenses were $78.1 million and $31.7 million for the years ended December 31, 2018 and 2017, respectively. While we expect our operating expenses to increase substantially in connection with our ongoing development activities related to our product candidates, we believe that these increases may be partially offset by the research funding in connection with a collaboration, option and license agreement we entered into in January 2019. We anticipate that our expenses will increase due to costs associated with our

clinical development program targeting in achromatopsia due to mutations in the *CNGB3* or *CNGA3* gene, inherited retinal dystrophy caused by mutations in *RPE65*, or RPE65-deficiency, and X-Linked retinitis pigmentosa, or XLRP. In addition, we expect to continue incurring increasing costs associated with our clinical activities for *hAQP1* for the treatment of radiation-induced xerostomia and xerostomia associated with Sjogren's syndrome. We are currently evaluating potential next steps for clinical development of AAV-GAD, which remains pending future discussions with regulatory agencies. We also expect to incur expenses related to research activities in additional therapeutic areas to expand our pipeline, hiring additional personnel in manufacturing, research, clinical trials, 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.

As a result of these anticipated expenditures, we 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 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, 2018 and after receiving an additional $77.4 million from a private placement of ordinary shares during the first quarter of 2019 and our receipt of the $100 million payment under the terms of the Collaboration Agreement, we estimate that such funds will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into 2022. 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. Our future capital requirements will depend on many factors, including:

- the initiation, progress, timing, costs and results of our planned clinical trials for our product candidates;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA, EMA and other regulatory authorities;
- the cost of 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 costs and timing of further developing our manufacturing facilities in the United Kingdom;
- the costs of operating as a public company.
- the extent to which we in-license or acquire other products 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.

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 Development

On October 5, 2018, we acquired Vector Neurosciences Inc. (“Vector”) and acquired Vector’s rights to the clinical stage gene therapy product candidate adeno-associated virus encoding glutamic acid decarboxylase (“AAV-GAD”), an investigational gene therapy medicine ready for continued Phase 2 clinical development for Parkinson’s disease. We issued an aggregate of 225,000 of our ordinary shares as initial merger consideration, consisting of 202,500 shares which were issued at the closing of the merger and an additional 22,500 shares to be issued 18 months following the closing.

On December 14, 2018, we acquired from Moorfields Eye Hospital NHS Foundation Trust of Moorfields Eye Hospital a long leasehold interest (the “Head Lease”) in the site of our manufacturing facility, 92 Britannia Walk, London N1 7LU, for a purchase price of approximately $6,615,000. As a result of this transaction, we are now the tenant under the Head Lease, which has a remaining term of 108 years, with no facility rent due.

In January and February, 2019, we amended and restated the following agreements: (i) the License Agreement, dated February 4, 2015, as amended, between Athena Vision Ltd. and UCLB; (ii) the License Agreement, dated July 28, 2017, as amended, between MeiraGTx UK II Limited and UCLB; and (iii) the License Agreement, dated March 15, 2018, among MeiraGTx Limited, MeiraGTx UK II Limited and UCLB to establish new stand-alone license agreements for our inherited retinal disease (“IRD”) programs. In connection with the stand-alone agreement related to CNGB3, we agreed to make an upfront payment to UCLB of £1,500,000 and issue £1,500,000 of our ordinary shares.

On January 30, 2019, we entered into a strategic collaboration with Janssen to develop and commercialize gene therapies for the treatment of inherited retinal diseases (IRDs). This Collaboration

Agreement provides for Janssen to pay us an $100 million upfront payment and provide us with research funding, and we are eligible to receive potential milestone payments and royalties. We will collaborate with Janssen to develop our current clinical programs in Retinitis Pigmentosa and two genetic forms of Achromatopsia and Janssen has the exclusive right to commercialize these products globally. We will manufacture these products for commercial supply. Janssen will pay 100% of the clinical and commercialization costs of the products and we are eligible to receive untiered 20 percent royalties on net sales of products and additional development and commercialization milestones of up to $340 million. In addition, we will enter a research collaboration with Janssen in the area of IRDs, 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 IND. Janssen will then pay 100% of the clinical and commercialization costs for these products and we will receive an untiered royalty in the high teens on net sales as well as development milestones. In addition, we have entered into a manufacturing research collaboration with Janssen to further develop processes for manufacturing AAV viral vectors in which the costs of the research will be shared.

On March 1, 2019, we consummated a private placement with various investors, including one of our existing shareholders Perceptive Life Sciences Master Fund Ltd., pursuant to which we issued and sold an aggregate of 5,797,102 ordinary shares for gross proceeds of approximately $80.0 million. The financing was led by JJDC, the investment arm of Johnson & Johnson, which made a $40.0 million equity investment in the Company and received 2,898,550 ordinary shares.

Components of Our Results of Operations

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, 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 facility.

We expense research and development costs as incurred.

We typically use our employee and infrastructure resources across our development programs. We track outsourced development costs by product candidate or development program, but we do not allocate personnel costs, license payments made under our licensing arrangements or other internal costs to specific development programs or product candidates. These costs are included in other research and development expenses in the table below.

The following table summarizes our research and development expenses:

	Year Ended December 31,		
	2018	2017	Change
Ophthalmology programs	$ 7,069,280	$ 4,133,015	$ 2,936,265
Salivary gland programs	1,136,355	913,706	222,649
Neurodegenerative diseases programs	5,164,761	2,220,843	2,943,918
Manufacturing	5,224,272	3,213,861	2,010,411
Other research and development costs	15,025,555	11,878,287	3,147,268
Total research and development expenses	$33,620,223	$22,359,712	$11,260,511

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 and continue to discover and develop additional product candidates. This increase in research and development costs may be partially offset by the research funding provided in connection with the Collaboration Agreement we entered into in January 2019

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 and MeiraGTx B.V. are measured using the foreign subsidiaries' local currency as the functional currency. MeiraGTx UK II 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 statement 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 date. 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 statement of operations and comprehensive loss.

Convertible note inducement expense

Convertible note inducement expense consists of the issuance of a warrant to a convertible note holder as an inducement to convert the note payable into Series C preferred shares.

Change in fair value of warrant liability

We have determined that our warrants are classified as liabilities on our balance sheet because the Preferred Shares underlying the warrants have a redemption feature in the event of a change of control of the Company. The fair values of the warrants are estimated using the Black-Scholes valuation model with certain assumptions regarding risk free interest rate, expected volatility, expected divided yield and expected life. The Black-Scholes value of the warrants was recorded as a warrant liability and is remeasured quarterly. Any changes in the quarterly valuation of the warrants is charged to operations.

Income Taxes

The 2018 income tax provision consisted of current tax expense of $0 and a deferred tax benefit of $474,391. The 2018 deferred tax benefit includes a $474,391 benefit recorded due to the required intraperiod tax allocation resulting from the loss from continuing operations and other comprehensive income.

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of our financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

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.

Consolidation

The accompanying consolidated financial statements include the accounts of Meira Holdings and its wholly owned subsidiaries:

MeiraGTx Limited, a limited company under the laws of England and Wales ("Meira Limited);

MeiraGTx, LLC, a Delaware corporation ("Meira LLC");

BRI-Alzan, Inc., a Delaware corporation ("BRI-Alzan");

MeiraGTx B.V., a Netherlands corporation ("Meira BV");

MeiraGTx Neurosciences, Inc. a Delaware corporation ("Meira Neuro");

MeiraGTx UK II Limited, ("Meira UK II"), a limited company under the laws of England and Wales; and

MeiraGTx UK Limited ("Meira UK"), a limited company under the laws of England and Wales.

All intercompany balances and transactions between the consolidated companies have been eliminated in consolidation.

Foreign Currencies

Our consolidated financial statements are presented in U.S. dollars, our reporting currency. The financial position and results of operations of MeiraGTx UK II and MeiraGTx UK II cash accounts holding U.S. dollars are remeasuring 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. 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 recording directly as a separate component of shareholders' equity and as other comprehensive loss on the consolidated statements of operations and comprehensive loss.

Income Taxes

Since we have recurring losses and a valuation allowance against deferred tax assets, there was no tax expense (benefit) through December 31, 2017. For the year ended December 31, 2018, we recognized a tax benefit of $(474,391). As of December 31, 2018, we had federal and state net operating loss ("NOL") carryforwards in the United States of approximately $14.2 million and $14.2 million respectively, and in the U.K. of approximately $94.1 million, which are available to reduce future taxable income. The U.S. federal and state NOL carryforwards incurred prior to January 1, 2018 in the amount of approximately $6.8 million and $6.7 million, respectively, will begin to expire in 2036. The U.S. NOL incurred after December 31, 2017 and the U.K. NOL will be indefinitely carried forward. As of December 31, 2018, we also had orphan drug and research and development credits in the U.S. in the amount of $1.1 million, which will begin to expire 2036.

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. Refundable research and development 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 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.

As of January 1, 2016, we early adopted ASU 2016-09, Improvements to Employee Share-Based Payment Accounting, and accounts for forfeitures as they occur from that date. Additionally, excess tax benefits and deficiencies will be recognized as income tax expense or benefit in the income statement. There was no cumulative effect adjustment as we did not issue any options prior to January 1, 2016.

We had accounted for options granted to non-employee consultants under ASC 505-50, Equity-Based Payments to Non-Employees. As such, we estimate the fair value of each such option using the Black-Scholes model, with the expected term of share options granted to non-employees initially equal to the options' maximum contractual life of ten years, at issuance. On each subsequent reporting date until performance is complete, we revalue all outstanding options granted to non-employee consultants during the vesting period of each tranche. Under ASC 505-50, upon re-measurement of each award, income or expense is recognized during its vesting term. Compensation cost relating to awards with service-based graded vesting schedules is recognized as general and administrative and research and development expenses in the consolidated statement of operations and comprehensive loss using the straight-line method. On July 1, 2018, we early adopted ASU 2018-07, Improvements to Nonemployee Share-Based Payment Accounting, which simplifies the accounting for share-based payments granted to nonemployees for goods and services. The adoption did not have a material effect on the consolidated financial statements.

Restricted Shares

In connection with certain service agreements and research agreements, we have granted restricted ordinary shares as compensation. The shares are recognized in the statement of operations and comprehensive loss based on their grant date fair values. Compensation cost relating to share grants with service-based graded vesting schedules is recognized based on the vesting schedule.

Results of Operations

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017, respectively

	2018	2017	Change
Operating expenses:			
General and administrative	$ 44,483,938	$ 9,325,017	$ 35,158,921
Research and development	33,620,223	22,359,712	11,260,511
Total operating expenses	78,104,161	31,684,729	46,419,432
Loss from operations	(78,104,161)	(31,684,729)	(46,419,432)
Other non-operating income (expense)			
Other income	83,075	—	83,075
Foreign currency (loss) gain	(3,824,383)	1,676,117	(5,500,500)
Convertible note inducement expense	—	(553,500)	553,500
Change in fair value of warrant liability	(1,514,775)	(465,633)	(1,049,142)
Interest income	53,408	26,073	27,335
Interest expense	(33,429)	(42,863)	9,434
Loss before income taxes	(83,340,265)	(31,044,535)	(52,295,730)
Benefit for income taxes	474,391	—	474,391
Net loss	$(82,865,874)	$(31,044,535)	$(51,821,339)

General and Administrative Expenses

General and administrative expenses were $44.5 million for the year ended December 31, 2018, compared to $9.3 million for the year ended December 31, 2017. The increase of $35.2 million was primarily due to increases of $19.7 million in payroll, $14.0 million in share-based compensation, $1.1 million in legal, $0.7 million in insurance $0.5 million in accounting, $0.4 million in travel, and $0.3 million in investor relations, which was partially offset by a decrease of $1.5 million in rent.

Research and Development Expenses

Research and development expenses for the year ended December 31, 2018 were $33.6 million, compared to $22.4 million for the year ended December 31, 2017. The increase of $11.2 million was primarily due to an increase in costs of $3.0 million for clinical trial costs related to our ophthalmology programs, $3.0 million for acquired neurology research and development, $2.3 million related costs of payroll and consultants, $1.6 million of depreciation, $1.3 million related to the preparation for production of our manufacturing facility, $1.0 million in share-based compensation, and $0.7 million in rent, which was partially offset an increase of $1.7 million in the research and development credit in the United Kingdom in 2018.

Foreign Currency (Loss) Gain

Foreign currency loss was $3.8 million for the year ended December 31, 2018 compared to a gain of $1.7 million for the year ended December 31, 2017. The change of $5.5 million was primarily due to a strengthening of the U.S. dollar against the pound sterling in 2018.

Convertible Note Inducement Expense

We recorded a $0.5 million convertible note inducement expense for the year ended December 31, 2017 primarily due to the issuance of a warrant to purchase 231,898 Convertible Preferred C Shares in 2017 to a convertible noteholder as an inducement to convert the note into Convertible Preferred C Shares.

Change in Fair Market Value of Warrant Liability

We recorded $1.5 million change in fair value of a warrant liability for the year ended December 31, 2018, compared to $0.5 million for the year ended December 31, 2017. The increase of $1.0 million was primarily due to the revaluation of certain warrants, which were issued to certain investors in September and November 2017, using the Black-Scholes valuation model at June 7, 2018, when the warrants were exercised and December 31, 2017.

Income Taxes

The 2018 income tax provision consisted of current tax expense of $0 and a deferred tax benefit of $474,391. The 2018 deferred tax benefit includes a $474,391 benefit recorded due to the required intraperiod tax allocation resulting from the loss from continuing operations and other comprehensive income.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. We have not generated positive cash flows from operations, and 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 product manufactured to support preclinical studies and clinical trials, expanding our intellectual property portfolio, and providing general and administrative support for our operations. As a result, 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 are required to maintain a stand-by letter of credit as a security deposit under a certain lease with ARE, an entity that is under common control with an entity that is a minority shareholder of the Company and whose executive chairman and founder is on our board of directors. Our bank requires us to maintain restricted cash balances to serve as collateral for the letter of credit issued to the landlord by the bank. As of December 31, 2018, the restricted cash balances for the ARE lease was invested in a commercial money market account. The restricted cash balance for the ARE lease remains at $123,376 through the end of the lease term in December 2021, plus three months. We had $123,376 of restricted cash included in long-term assets as of December 31, 2018. 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 the sale of our ordinary shares and Convertible Preferred C Shares. In January 2019, we entered into the Collaboration Agreement, which provides for Janssen to pay us an $100 million upfront payment and provide us with research funding, and we are eligible to receive potential milestone payments and royalties.

Cash Flows

We had $68.1 million and $8.5 million of cash and cash equivalents as of December 31, 2018 and 2017, respectively.

The following table summarizes our sources and uses of cash for the period presented:

	For the year ended December 31, 2018	2017
Net cash used in operating activities	$ (58,887,870)	$(18,055,386)
Net cash used in investing activities	(11,258,479)	(10,535,717)
Net cash provided by financing activities	130,040,415	19,340,215
Increase (decrease) in cash	$ 59,894,066	$ (9,250,888)

Operating Activities

During the year ended December 31, 2018, our cash used in operating activities of $58.9 million was primarily due to our net loss of $82.9 million as we incurred expenses associated with research activities on our clinical programs and research activities for our other product candidates and incurred general and administrative expenses. The loss included non-cash charges of $27.9 million, which consisted of $18.1 million of share-based compensation, issuance of shares for acquired research and development in the amount of $3.0 million, change in fair value of warrant liability in the amount of $1.5 million, depreciation of $2.1 million, and a foreign currency loss of $3.9 million, which was partially offset by an income tax benefit of $0.5 million. Additionally, current assets, consisting of prepaid expenses, other current assets and security deposits increased by $3.9 million. Current liabilities, consisting of accounts payable, accrued expenses, deferred rent, due to affiliate and other liabilities, decreased by $0.1 million

During the year ended December 31, 2017, our cash used in operating activities of $18.1 million was primarily due to our net loss of $31.0 million as we incurred expenses associated with research activities on our clinical programs and research activities for our other product candidates and incurred general and administrative expenses. The loss included non-cash charges of $3.0 million, which consisted of $3.0 million of share-based compensation, change in fair value of warrant liability in the amount of $0.5 million, convertible note inducement expense of $0.5 million and depreciation of $0.7 million, which was partially offset by a foreign currency gain of $1.7 million. Additionally, current liabilities, consisting of accounts payable, accrued expenses deferred rent, and due to affiliate, increased by $11.1 million. Current assets, consisting of prepaid expenses and other current assets, decreased by $1.2 million.

Investing Activities

Net cash used in investing activities for the years ended December 31, 2018 and December 31, 2017 of $11.3 million and $10.5 million, respectively, consisted of purchase of property plant and equipment, primarily for our manufacturing facility.

Financing Activities

Net cash provided by financing activities was $130.0 million for the year ended December 31, 2018, represented proceeds of $65.6 million from the issuance of Ordinary Shares in connection with our initial public offering, $56.1 million from the issuance of Convertible Preferred C Shares and $9.7 million from the exercise of warrants, which was partially offset by the repayment of a note payable in the amount of $1.4 million.

Net cash provided by financing activities was $19.3 million for the year ended December 31, 2017, represented proceeds of $16.8 million from the issuance of Convertible Preferred C Shares and $2.5 million from the issuance of a note payable

Funding Requirements

Our operating expenses increased substantially in 2018 and 2017 and are expected to increase substantially in the future in connection with our ongoing activities, particularly as we advance our clinical activities including scale-up of manufacturing processes and additional clinical trials. In addition, we expect to continue to incur additional costs associated with operating as a public company.

Specifically, our expenses will increase as we:

- pursue the preclinical and clinical development of our product candidates;
- scale up our manufacturing processes and capabilities to support our preclinical studies and clinical trials of our product candidates;
- in-license or acquire the rights to other products, product candidates or technologies;
- maintain, expand and protect our intellectual property portfolio;
- hire additional personnel in research, manufacturing and regulatory and clinical development as well as management personnel; and
- continue to expand our operational, financial and management systems and increase personnel, including personnel to support our operations as a public company.

Based on our planned use of the net proceeds of the IPO, our current cash and cash equivalents, the proceeds from a private placement of ordinary shares in March 2019 and the proceeds we are to receive pursuant to the terms of the Collaboration Agreement, we estimate that such funds will be sufficient to enable us to fund our operating expenses and capital expenditure requirements. 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.

Because of the numerous risks and uncertainties associated with research, development and commercialization of gene therapies, it is difficult to estimate with certainty the amount of our working capital requirements. Our future funding requirements will depend on many factors, including:

- the progress, costs and results of our preclinical development and initial clinical trials for our gene therapy programs;
- the progress, costs and results of our additional clinical, research and preclinical development programs in gene therapy;
- the costs and timing of process development and manufacturing scale-up activities associated with our clinical programs;
- our ability to establish and maintain strategic collaborations, licensing or other agreements and the financial terms of such agreements;
- the scope, progress, results and costs of any product candidates that we may derive from our platform technology or any other product candidates that we may develop;
- the extent to which we in-license or acquire rights to other products, product candidates or technologies; and
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against any intellectual property-related claims.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaboration agreements, other third-party funding, strategic alliances, licensing arrangements and marketing and distribution arrangements.

To the extent that we raise additional capital through the sale of equity or convertible debt 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 holder of ordinary shares. Debt financing and preferred equity 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. If we raise additional funds through other third-party funding, collaboration agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, 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 or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following is a summary of our significant contractual obligations as of December 31, 2018.

		Payments by Period			
	Total	Less Than 1 Year	More Than 1 Year and Less Than 3	More Than 3 Years and Less Than 5	More Than 5 Years
Operating leases	4,615,676	889,465	1,828,838	700,569	1,196,805
Capitalized leases	35,894	35,894	—	—	—
	4,651,570	925,359	1,828,838	700,569	1,196,805

(1) Represents the leases for office, laboratory, and manufacturing space in London, United Kingdom and New York, New York under non-cancelable operating leases that expire between December 2021 and May 2027 and December 2021.
(2) Represents future payments under capitalized leases for office equipment.

The contractual obligations table does not include any potential future payments we may be required to make under (1) our license agreements with UCLB, Brandeis and other entities or (2) our sponsored research agreements with universities and commercial research organizations. These agreements may be terminated upon 30-90 days written notice and, therefore, the amounts to be paid by us are not fixed or determinable at this time.

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.

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. However, relative to foreign currency exposures as of December 31, 2018, a 10% unfavorable movement in foreign currency exchange rates would not expose us to a significant increase in net loss. We had cash and cash equivalents of $68.1 million as of December 31, 2018, which consist of non-interest-bearing bank deposits. Other than accounts payable and accrued expenses incurred in the ordinary course of business, we had no other debt outstanding as of December 31, 2018. We had cash and cash equivalents of $8.5 million as of December 31, 2017, which consist of bank deposits and money market funds. Such interest-earning instruments carry a degree of interest rate risk; however, historical fluctuations in interest income have not been significant for us. Other than accounts payable and accrued expenses incurred in the ordinary course of business, we had a note payable of $1.4 million as of December 31, 2017.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS
MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
FOR THE YEARS ENDED DECEMBER 31, 2018 AND 2017

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, 2018 and 2017, the related consolidated statements of operations and comprehensive loss**,** shareholders' deficit and cash flows for each of the two years in the period ended December 31, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, 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.

Stamford, Connecticut
March 26, 2019

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED BALANCE SHEETS

	December 31, 2018	December 31, 2017
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 68,080,175	$ 8,548,638
Prepaid expenses	1,937,785	1,961,243
Other current assets	4,634,105	965,233
Total Current Assets	74,652,065	11,475,114
Property, plant and equipment, net	22,014,237	14,255,729
Security deposits	105,085	—
Restricted cash	123,376	123,376
TOTAL ASSETS	$ 96,894,763	$ 25,854,219
LIABILITIES, CONVERTIBLE PREFERRED C SHARES AND SHAREHOLDERS' EQUITY (DEFICIT)		
CURRENT LIABILITIES:		
Accounts payable	$ 3,042,861	$ 7,055,380
Accrued expenses	11,991,697	9,332,944
Note payable	—	1,442,009
Warrant liability	—	2,679,633
Capitalized lease obligation—current portion	27,199	30,850
Due to Kadmon	—	861,030
Other current liabilities	437,053	—
Total Current Liabilities	15,498,810	21,401,846
Capitalized lease obligation	7,097	34,298
Deferred rent	201,264	266,290
Asset retirement obligation	128,119	178,419
TOTAL LIABILITIES	15,835,290	21,880,853
COMMITMENTS		
CONVERTIBLE PREFERRED C SHARES		
Convertible Preferred C Shares 0 and 5,005,935 outstanding at December 31, 2018 and December 31, 2017, respectively (liquidation preference of $52,455,700 at December 31, 2017)	—	51,338,631
SHAREHOLDERS' EQUITY (DEFICIT):		
Ordinary Shares, $0.00003881 nominal value, 1,288,327,750 authorized 27,386,632 issued and outstanding at December 31, 2018 8,826,190 issued and 8,714,563 issued and outstanding at December 31, 2017	1,064	342
Capital in excess of nominal value	229,054,460	20,080,713
Accumulated other comprehensive income (loss)	293,666	(2,022,477)
Accumulated deficit	(148,289,717)	(65,423,843)
Total Shareholders' Equity (Deficit)	81,059,473	(47,365,265)
TOTAL LIABILITIES, CONVERTIBLE PREFERRED C SHARES AND SHAREHOLDERS' EQUITY (DEFICIT)	$ 96,894,763	$ 25,854,219

See Notes to Consolidated Financial Statements

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

	For the Year Ended December 31, 2018	2017
Operating expenses:		
General and administrative	$ 44,483,938	$ 9,325,017
Research and development	33,620,223	22,359,712
Total operating expenses	78,104,161	31,684,729
Loss from operations	(78,104,161)	(31,684,729)
Other non-operating income (expense):		
Other income	83,075	—
Foreign currency (loss) gain	(3,824,383)	1,676,117
Convertible note inducement expense	—	(553,500)
Change in fair value of warrant liability	(1,514,775)	(465,633)
Interest income	53,408	26,073
Interest expense	(33,429)	(42,863)
Loss before income taxes	(83,340,265)	(31,044,535)
Benefit for income taxes	474,391	—
Net loss	(82,865,874)	(31,044,535)
Other comprehensive income (loss):		
Foreign currency translation, net of tax of $474,391 and $0 in 2018 and 2017, respectively	2,316,143	(1,361,365)
Total comprehensive loss	$(80,549,731)	$(32,405,900)
Net loss	$(82,865,874)	$(31,044,535)
Accretion on convertible preferred C shares and warrants	(1,806,512)	(806,963)
Adjusted net loss	$(84,672,386)	$(31,851,498)
Basic and diluted net loss per ordinary share	$ (4.47)	$ (3.72)
Weighted-average number of ordinary shares outstanding	18,948,520	8,572,315

See Notes to Consolidated Financial Statements

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED C SHARES AND SHAREHOLDERS' EQUITY (DEFICIT)
AS OF DECEMBER 31, 2018

	Convertible Preferred C Shares		Shareholders' Equity (Deficit)					
	Shares	Amount	Ordinary Shares	Amount	Capital in Excess of Nominal Value	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Shareholders' Equity (Deficit)
Balance at December 31, 2016	1,574,739	$ 32,833,660	8,818,461	$ 342	$ 17,900,995	$ (661,112)	$ (34,379,308)	$ (17,139,083)
Exercised stock options	—	—	1,288	—	9,950	—	—	9,950
Issuance of A ordinary shares in connection with a license agreement	—	—	6,441	—	17,000	—	—	17,000
Extinguishment of convertible preferred C shares, net of unaccreted issuance costs	(1,584,469)	(33,115,157)	—	—	33,115,157	—	—	33,115,157
Issuance of convertible preferred C shares in connection with extinguishment	3,168,929	33,206,360	—	—	(33,206,360)	—	—	(33,206,360)
Conversion of note payable into convertible preferred C shares	238,579	2,500,000	—	—	—	—	—	—
Issuance of convertible preferred C shares, net of warrants and issuance costs	1,608,157	15,198,008	—	—	—	—	—	—
Accretion of issuance costs on convertible preferred C shares	—	100,760	—	—	(100,760)	—	—	(100,760)
Accretion of warrants issued in connection with convertible preferred C shares	—	615,000	—	—	(615,000)	—	—	(615,000)
Share-based compensation	—	—	—	—	2,959,731	—	—	2,959,731
Foreign currency translation	—	—	—	—	—	(1,361,365)	—	(1,361,365)
Net loss for the year ended December 31, 2017	—	—	—	—	—	—	(31,044,535)	(31,044,535)
Balance at December 31, 2017	5,005,935	$ 51,338,631	8,826,190	$ 342	$ 20,080,713	$(2,022,477)	$ (65,423,843)	$ (47,365,265)
Issuance of convertible preferred C shares in connection with payables	129,419	1,356,129	—	—	—	—	—	—
Issuance of convertible preferred C shares in connection with a license agreement	13,360	140,000	—	—	—	—	—	—
Sale of convertible preferred C shares, net of issuance costs	5,425,124	56,159,119	—	—	—	—	—	—
Accretion of issuance costs on convertible preferred C shares	—	761,012	—	—	(761,012)	—	—	(761,012)
Accretion of warrants issued in connection with convertible preferred C shares	—	1,045,500	—	—	(1,045,500)	—	—	(1,045,500)
Exercise of warrants	927,594	9,720,000	—	—	4,194,408	—	—	4,194,408
Conversion of convertible preferred C shares into A ordinary shares	(11,501,432)	(120,520,391)	11,501,432	446	120,519,945	—	—	120,520,391
Sale of ordinary shares in initial public offering, net of issuance costs of $9,807,622	—	—	5,000,000	194	65,192,184	—	—	65,192,378
Issuance of ordinary shares in connection with Vector Neurosciences acquisition			202,500	9	2,990,241	—	—	2,990,250
Share-based compensation	—	—	1,856,510	73	17,883,481	—	—	17,883,554
Foreign currency translation, net of income taxes	—	—	—	—	—	2,316,143	—	2,316,143
Net loss for the year ended December 31, 2018	—	—	—	—	—	—	(82,865,874)	(82,865,874)
Balance at December 31, 2018	—	$ —	27,386,632	$1,064	$229,054,460	$ 293,666	$(148,289,717)	$ 81,059,473

See Notes to Consolidated Financial Statements

MEIRAGTX HOLDINGS PLC AND SUBSIDIARIES
CONSOLIDATED STATEMENTS OF CASH FLOWS

	For the Year Ended December 31, 2018	2017
Cash flows from operating activities:		
Net loss	$ (82,865,874)	$(31,044,535)
Adjustments to reconcile net loss to net cash used in operating activities:		
Preferred C shares issued in connection with a license agreement	140,000	—
Issuance of shares for services	—	17,000
Share-based compensation expense	17,883,554	2,959,731
Foreign currency loss (gain)	3,824,383	(1,676,117)
Depreciation	2,053,220	679,177
Amortization of interest on asset retirement obligation	(38,301)	19,313
Change in fair value of warrant liability	1,514,775	465,633
Convertible note inducement expense	—	553,500
Issuance of shares for acquired research and development expense	2,990,250	—
Issuance of note payable in connection with lease termination	—	1,442,009
Benefit for income taxes	(474,391)	—
(Increase) in operating assets:		
Prepaid expenses	(35,465)	(669,756)
Other current assets	(3,684,465)	(493,424)
Security deposits	(115,573)	—
Increase (decrease) in operating liabilities:		
Accounts payable	(2,119,493)	4,728,491
Accrued expenses	2,529,568	4,969,619
Due to Kadmon	(861,030)	317,992
Other liabilities	436,161	—
Deferred rent	(65,189)	(324,019)
Net cash used in operating activities	(58,887,870)	(18,055,386)
Cash flows from investing activities:		
Purchase of property, plant and equipment	(11,258,479)	(10,535,717)
Net cash used in investing activities	(11,258,479)	(10,535,717)
Cash flows from financing activities:		
Payments on capitalized lease obligation	(30,852)	(24,388)
Exercise of warrants	9,720,000	—
Proceeds from the sale of ordinary shares	69,750,000	—
Issuance costs in connection with ordinary shares	(4,115,843)	—
Issuance costs in connection with convertible preferred C shares	(690,475)	—
Proceeds from the sale of convertible preferred C shares	56,849,594	16,854,653
(Payment) issuance of note payable	(1,442,009)	2,500,000
Proceeds from excercised stock options	—	9,950
Net cash provided by financing activities	130,040,415	19,340,215
Net increase (decrease) in cash, cash equivalents and restricted cash	59,894,066	(9,250,888)
Effect of exchange rate changes on cash	(362,529)	1,417
Cash, cash equivalents and restricted cash at beginning of year	8,672,014	17,921,485
Cash, cash equivalents and restricted cash at end of year	$ 68,203,551	$ 8,672,014
Supplemental disclosure of non-cash transactions:		
Fixed asset acquisition included in accounts payable and accrued expenses at end of year	$ 293,051	$ 415,650
Issuance of convertible preferred C shares in connection with payables	$ 1,356,129	$ —
Conversion of convertible preferred C shares into ordinary shares	$120,520,391	$ —
Reclassification of warrant liability upon exercise of warrants	$ 4,194,408	$ —
Capitalized lease obligation for equipment purchase	$ —	$ 78,063
Issuance costs in connection with sale of ordinary shares in accounts payable and accrued expenses at end of period	$ 441,779	$ —
Conversion of note payable into convertible preferred C shares	$ —	$ 2,500,000
Asset retirement obligation in connection with a lease	$ (29,804)	$ (75,011)
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 34,546	$ 20,894

See Notes to Consolidated Financial Statements

1. Principal Business Activity:

The Company

MeiraGTx Holdings plc (the "Company" or "Meira Holdings"), a limited company under the laws of the Cayman Islands, is a clinical-stage biotech company developing novel gene therapy treatments for a wide range of inherited and acquired disorders for which there are no effective treatments available. The Company is focused on developing therapies for ocular diseases, including rare inherited blindness as well as Xerostomia following radiation treatment for head and neck cancers and neurodegenerative diseases such as amyothrophic lateral sclerosis ("ALS") and Parkinson's disease ("PD").

Reorganization and Initial Public Offering

We commenced operations as MeiraGTx Limited, a private limited company incorporated under the laws of England and Wales in 2015. On May 28, 2018, the Board of Directors of MeiraGTx Limited approved the Reorganization Transactions, effective June 7, 2018, pursuant to which the Board of Directors approved the transfer of the shares held by each of the MeiraGTx Limited's shareholders for the equivalent class and number of shares issued by Meira Holdings. On June 7, 2018, the Company completed its initial public offering ("IPO"), selling 5,000,000 ordinary shares ("Ordinary Shares") at a public offering price of $15.00 per share, and receiving $65.2 million in net proceeds, after deducting underwriting discounts and commissions and offering expenses payable by us.

Reverse Share Split

On June 7, 2018 MeiraGTx Limited's Board of Directors and shareholders approved a 1:3.881 reverse share split. All share information presented in these financial statements and accompanying footnotes have been retroactively adjusted to reflect the decreased number of shares resulting from this action.

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, 2018 totaled $(148,289,717), 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; dependence on third parties; and dependence on key personnel. The Company has not generated positive cash flows from operations, and 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, 2018, the Company had cash and cash equivalents in the amount of $68,080,175, which consisted of depository accounts. On January 30, 2019, the Company entered into a collaboration, option and license agreement with Janssen Pharmaceuticals, Inc., one of the Janssen Pharmaceuticals Companies of Johnson & Johnson (the "Collaboration Agreement"). Under the terms of the Collaboration Agreement, the Company will receive an upfront payment of $100 million. The Company will also receive research 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. On February 27, 2019, the Company issued 5,797,102 ordinary shares in an $80 million private placement led by JJDC, Inc., the investment arm of Johnson & Johnson, (the "Private Placement") for net proceeds of $77.4 million. The Company estimates that its cash and cash equivalents on hand at December 31, 2018 as well as proceeds from the Collaboration Agreement and the Private Placement will be sufficient to cover its expenses for at least the next twelve months from the date of issuance of these 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.

The Company's limited capital resources and operations to date have been funded primarily with the proceeds from private equity offerings and the IPO. 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.

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 under the laws of England and Wales ("Meira Limited);
MeiraGTx, LLC, a Delaware corporation ("Meira LLC");
BRI-Alzan, Inc., a Delaware corporation ("BRI-Alzan");
MeiraGTx B.V., a Netherlands corporation ("Meira BV");
MeiraGTx Neurosciences, Inc. a Delaware corporation ("Meira Neuro");
MeiraGTx UK II Limited, ("Meira UK II"), a limited company under the laws of England and Wales; and
MeiraGTx UK Limited ("Meira UK"), a limited company under the laws of England and Wales.

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: valuation of A ordinary shares ("A Ordinary Shares") issued prior to the Company's initial public offering, the accounting for research and development costs, warrants, share-based compensation and accrued expenses.

Subsequent Events

The Company considers events or transactions that occur after the balance sheet date but before the financial statements are issued to provide additional evidence relative to certain estimates or to identify matters that require additional disclosure. The Company evaluated all events and transactions through March 26, 2019, the date these consolidated financial statements were issued. See Note 18 for additional information.

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 deposits that are readily convertible into cash.

Warrant Liability

During 2017, the Company issued warrants to purchase Convertible Preferred C Shares (the "Preferred Shares") to certain investors. Due to the potential redemption feature of the underlying Preferred Shares, the warrants had been classified as a liability. Liability accounting requires that the fair value of warrants be remeasured each reporting period with changes recorded in the statements of operations and comprehensive loss. These Preferred Shares warrants remained outstanding until their exercise in June 2018, at which time the warrant liability was remeasured to fair value and reclassified to additional paid-in capital.

Financial Instruments

The carrying value of prepaid expenses, other current assets, accounts payable, accrued expenses, notes payable and amounts due to an affiliate reported in the consolidated balance sheets equal or approximate fair value due to their short maturities.

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 our 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:

		Fair Value Measurement Using:		
Description	December 31, 2018	Significant Observable Inputs (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable (Level 3)
Restricted cash	$ 123,376	$123,376	$—	$ —

		Fair Value Measurement Using:		
Description	December 31, 2017	Significant Observable Inputs (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable (Level 3)
Restricted cash	$ 123,376	$123,376	$—	$ —
Warrants	$2,679,633	$ —	$—	$2,679,633

The table below represents a rollforward of the assets and liabilities that are required to be measured at fair value on a recurring basis from December 31, 2016 to December 31, 2018:

	Significant Observable Inputs (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Balance as of December 31, 2016	$ 444,844	$—	$ —
Cash released from restriction	(321,468)	—	—
Fair value of warrants issued	—	—	2,214,000
Change in fair value of warrants	—	—	465,633
Balance as of December 31, 2017	123,376	—	2,679,633
Change in fair value of warrants			1,514,775
Exercise of warrants	—	—	(4,194,408)
Balance as of December 31, 2018	$ 123,376	$—	$ —

The warrants were classified as liabilities because the underlying Preferred Shares had a redemption feature in the event of a change of control of the Company. On June 5, 2018, the warrants were exercised at which time the warrant liability was determined to be $4,194,408, which represented the difference in the market value of the Preferred Shares and the exercise price of the warrants. This resulted in an increase of the warrant liability in the amount of $1,514,775 for the year ended December 31, 2018. The related warrant liability of $4,194,408 was reclassified as Capital in Excess of Nominal Value at such time.

The fair values of the warrants were estimated using the Black-Scholes valuation model with the following assumptions:

	June 4, 2018	December 31, 2017	September 21, 2017
Risk-free interest rate	1.77%	1.72%	1.38%
Expected volatility	80%	80%	80%
Expected dividend yield	0	0	0
Expected life	1 day	9 months	18 months

For the unobservable inputs for the warrants, the expected volatility was determined at each measurement date by taking an average of the volatility of other publicly-traded peer biotechnology companies. The expected life was determined at each measurement date based upon the Company's estimate of the time until the Company has a conversion event, as described in Note 12.

The fair value of the Preferred Shares were based upon recent issuances of the Company's Preferred Shares on or about those dates.

The estimated fair values of the Company's warrants were not necessarily indicative of the amounts that would have been realized in a current market exchange. The determination of the fair value of the warrants were sensitive to changes in the assumptions used and a change in those inputs could result in a significantly higher or lower fair value measurement. If the volatility were to increase or the expected life were to increase, the fair value of the warrant would increase. Conversely, if the volatility were to decrease or the expected life were to decrease, the fair value of the warrant would decrease.

Convertible Preferred C Shares

The Preferred Shares were not redeemable, except in the event of a change of control which was outside the control of the Company and required shareholder approval. The redemption value of the Preferred Shares upon a change in control is equal to its liquidation value described below.

The Company is accounting for its Preferred Shares under the requirements of ASC 480, *Distinguishing Liabilities from Equity,* which establishes standards for how an issuer classifies and measures certain financial instruments with characteristics of both liabilities and equity. The carrying value of the Preferred Shares is presented as temporary equity and is increased by periodic accretions so that the carrying amount will equal the redemption amount at the estimated date that the Preferred Shares will be converted into Ordinary Shares. These increases are affected through charges against additional paid-in capital, to the extent it is available, or accumulated deficit. For all Preferred Shares issuance, the difference between the amount invested by the holders of the Preferred Shares, net of issuance costs and the initial fair value of warrants issued in connection with the Preferred Shares (if applicable), and the liquidation value of the Preferred Shares is recorded as accretion over the estimated life of the Preferred Shares. The accretion is added to net loss to arrive at the net loss available to Ordinary Shareholders in the calculation of loss per Ordinary Share.

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. 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.

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 life of the lease (see Note 5).

The estimated useful lives of the asset categories are set forth in the table below:

Asset Category	Useful Lives
Computer and office equipment	3 years
Laboratory equipment	5 years
Manufacturing equipment	7 years
Furniture and fixtures	5 years
Capitalized leasehold interest	25 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 recorded no impairment charges in 2018 or 2017.

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 assumed to be 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 potential ordinary shares 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 (see Note 13).

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 14).

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, 2018 and 2017, the Company does not have any significant uncertain tax positions.

The Company is required to estimate income taxes in each of the jurisdictions in which it operates.

The Company's reserves related to taxes are based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings or positions is more likely than not to be realized. As of December 31, 2018, the Company had no unrecognized tax benefits or related interest and penalties accrued.

In the United States, on December 22, 2017, the "Tax Cuts and Jobs Act" (the "Act") was signed into law. Substantially all of the provisions of the Act are effective for taxable years beginning after December 31, 2017. The Act includes significant changes to the Internal Revenue Code of 1986 (as amended, the "Code"), including amendments which significantly change the taxation of individuals, and business entities. The Act contains numerous provisions impacting the Company, the most significant of which reduces the Federal corporate statutory tax rate from 34% to 21%.

The staff of the U.S. Securities and Exchange Commission ("SEC") has recognized the complexity of reflecting the impacts of the Act, and on December 22, 2017 issued guidance in Staff Accounting Bulletin 118 ("SAB 118"), which clarifies accounting for income taxes under ASC 740 if information is not yet available or complete and provides for up to a one year period in which to complete the required analyses and accounting (the measurement period). SAB 118 describes three scenarios (or "buckets") associated with a company's status of accounting for income tax reform: (1) a company is complete with its accounting for certain effects of tax reform, (2) a company is able to determine a reasonable estimate for certain effects of tax reform and records that estimate as a provisional amount, or (3) a company is not able to determine a reasonable estimate and therefore continues to apply ASC 740, based on the provisions of the tax laws that were in effect immediately prior to the Act being enacted.

The various provisions under the Act deemed most relevant to the Company have been considered in preparation of its financial statements as of December 31, 2017. The Company had made a reasonable estimate for certain effects of tax reform and had recorded provisional amounts as part of its income tax provision. To the extent that clarifications or interpretations materialized in the future that would impact upon the effects of the Act incorporated into the December 31, 2017 financial statements, those effects would have been reflected in the future as or if they materialize. As of December 31, 2018, the Company has completed its accounting for all of the tax effects of the Act. Based on the additional analysis performed, no adjustments to the provisional amounts were made in the reporting period which had an impact to the tax provision or consolidated financial statements.

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 manufacture 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. Refundable research and development credits / tax credits received 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 expense, as the case may be.

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 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 employees and members of the Company's board of directors 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.

As there had been no public market for the Company's Ordinary Shares until the Company's IPO on June 7, 2018, the estimated fair value of the Ordinary Shares until that time had been determined by the Company's board of directors as of the date of each option grant, with input from management, considering the most recently available third-party valuations of Ordinary Shares and the board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. The fair value of Ordinary Shares after the Company's IPO was determined based upon the closing share price on the date of grant.

The third party estimated the fair value of the equity using a special case of the market approach known as the backsolve method. The backsolve method was used to solve for the implied total equity value based on the Company's recent Series C financing round. Consideration was given to the rights and preferences of each of the Company's classes of equity and the expected time to a liquidity event. An option pricing allocation method, or OPM, was selected to allocate the total equity value. The OPM treats ordinary shares and preferred shares as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the Ordinary Shares have value only if the funds available for distribution to shareholders exceeded the value of the Preferred Shares' liquidation preference at the time of the liquidity event, such as a strategic sale or a merger. These third-party valuations resulted in a valuation of the Company's Ordinary Shares of $7.57, $2.64 and $5.63 per share as of December 31, 2016, September 15, 2017 and December 31, 2017, respectively.

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.

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

employees and members of the Company's board of directors 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 SEC's Staff Accounting Bulletin No. 107 and No. 110, *Share-Based Payment.*

Similarly, the Company believes that its future volatility will 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 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.

The Company accounted for options granted to non-employee consultants under ASC 505-50, *Equity-Based Payments to Non-Employees,* or ASC 505-50. As such, the Company estimates the fair value of each such option using the Black-Scholes model, with the expected term of share options granted to non-employees initially equal to the options' maximum contractual life of ten years, at issuance. On each subsequent reporting date until performance is complete, the Company revalued all outstanding options granted to non-employee consultants during the vesting period of each tranche. Under ASC 505-50, upon re-measurement of each award, income or expense is recognized during its vesting term. Compensation cost relating to awards with service-based graded vesting schedules is recognized as general and administrative and research and development expenses in the consolidated statements of operations and comprehensive loss using the straight-line method.

On July 1, 2018, the Company early adopted ASU 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU No. 2018-07") which simplifies the accounting for share-based payments granted to nonemployees for goods and services. The ASU supersedes ASC 505-50 and expands the scope of ASC 718 to include *all* share-based payment arrangements related to the acquisition of goods and services from both nonemployees and employees. The adoption of ASU No. 2018-17 did not have a material effect on the consolidated financial statements.

Restricted Shares

In connection with certain service agreements and research agreements, the Company has granted restricted Ordinary Shares as compensation. The Ordinary Shares are recognized in the consolidated statements of operations and comprehensive loss based on their grant date fair values. Compensation cost relating to share grants with service-based graded vesting schedules is recognized based on the vesting schedule.

Leases

The Company recognizes rent expense for operating leases on a straight-line basis over the term of the lease, beginning on the date the Company takes possession of the property. Rent expense includes the base amounts stated in the lease agreement as well as the effect of reduced or free rent and rent escalations. At lease inception, the Company determines the lease term by assuming the exercise of those renewal options that are reasonably assured because of the significant economic penalty that exists for not exercising those options. The expected lease term is one of the factors used to determine whether a lease is classified as an operating or capital lease and is used to calculate the straight-line rent expense. The difference between the cash paid to the landlord and the amount recognized as rent expense on a straight-line basis is included in deferred rent and classified within long-term liabilities. Lease incentives made by landlords to or on behalf of the Company for leasehold improvements are recorded as deferred rent and classified as long-term liabilities.

Asset Retirement Obligation

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, we estimate the fair value of our 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 our 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 amount of 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 folows:

	For the year ended December 31,	
	2018	2017
Balance at beginning of year	$178,419	$221,254
Inception of asset retirement obligation	69,286	—
Amortization of interest	(38,301)	19,313
Change in estimate	(99,090)	(75,011)
Effects of exchange rate	17,805	12,863
Balance at end of year	$128,119	$178,419

Other Comprehensive Income (Loss)

Other comprehensive income (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 income (loss) impacting the Company is foreign currency translation.

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 and Meira B.V. are measured using the foreign subsidiaries' local currency as the functional currency. Meira UK II's 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 sheets 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.

Segment Information

Management has concluded it has a single reporting segment for purposes of reporting financial condition and results of operations.

The following table summarizes non-current assets by geographical area:

	December 31, 2018	December 31, 2017
United States	$ 454,568	$ 436,463
United Kingdom	21,788,130	13,942,642
	$22,242,698	$14,379,105

Accounting Pronouncements Recently Adopted

In June 2018, the FASB issued ASU 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting,* which simplifies the accounting for share-based payments granted to nonemployees for goods and services. The ASU supersedes ASC 505-50 and expands the scope of ASC 718 to include *all* share-based payment arrangements related to the acquisition of goods and services from both nonemployees and employees. As a result, most of the guidance in ASC 718 associated with employee share-based payments, including most of its requirements related to classification and measurement, applies to nonemployee share-based payment arrangements. ASU 2018-07 generally requires an entity to use a modified retrospective transition approach, with a cumulative-effect adjustment to retained earnings as of the beginning of the period of adoption, for all (1) liability-classified nonemployee awards that have not been settled as of the adoption date and (2) equity-classified nonemployee awards for which a measurement date has not been established. The guidance is applicable to public business entities for fiscal years beginning after December 15, 2019 and interim periods within those years. Early adoption is permitted, and the Company adopted ASU No. 2018-07 on July 1, 2018, which did not have a material effect on the consolidated financial statements.

In January 2017, the FASB issued ASU No. 2017-01, *Business Combinations (Topic 805), Clarifying the Definition of a Business,* or ASU 2017-01*,* that clarifies the definition of a business to assist entities with evaluating whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. ASU 2017-01 requires an entity to evaluate if substantially all of the fair value of the gross assets acquired or disposed of is concentrated in a single identifiable asset or a group of similar identifiable assets; if so, the set of transferred assets and activities is not a business. ASU 2017-01 also requires a business to include at least an input and one substantive process that together significantly contribute to the ability to create output and removes the evaluation of whether a market participant could replace missing elements. ASU 2017-01 should be applied prospectively and is effective for annual periods beginning after December 15, 2017 and interim periods within those annual periods. The adoption of ASU 2017-01 on January 1, 2018 did not have a material effect on the Company's financial position, results of operations or cash flows.

In December 2016, the FASB issued ASU No. 2016-20, *Technical Corrections and Improvements to Topic 606, Revenue from Contracts with Customers,* or ASU 2016-20, that allows entities not to disclose variable consideration allocated to performance obligations related to either: (1) sales-or usage-based royalties on licenses of intellectual property or (2) variable consideration allocated entirely to a wholly unsatisfied performance obligation or to a wholly unsatisfied promise to transfer a distinct good or service that forms part of a single performance obligation when certain criteria are met. ASU 2016-20 also requires entities that use any of the new or previously existing optional exemptions to expand their qualitative disclosures. It also makes 12 additional technical corrections and improvements to the new revenue standard, ASU 2014-09. The amendments have the same effective date and transition requirements as ASU 2014-09. The adoption of ASU 2016-20 did not have a material effect on its financial position, results of operations or cash flows.

In November 2016, the Financial Accounting Standards Board, or FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230), Restricted Cash* (a consensus of the Emerging Issues Task Force), or ASU 2016-18, which changes the presentation of the cash flow statement to include amounts generally described as restricted cash or restricted cash equivalents, together with cash and cash equivalents, when reconciling the beginning-of-period and end-of-period amounts shown on the statement of cash flows. ASU 2016-18 also requires additional disclosures concerning the nature of the restrictions on cash and cash equivalents and a reconciliation between amounts of cash, cash equivalents and restricted cash on the balance sheet and statement of cash flows for each period presented. ASU 2016-18 will be applied retrospectively to all periods presented and is effective for public business entities for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. Early adoption is permitted, including adoption in an interim period. Prior to adoption, the Company presented changes in restricted cash as an operating activity in the statement of cash flows. Upon adoption of ASU 2016-18 on January 1, 2018, such changes are now reflected in the beginning and ending balances of cash, cash equivalents and restricted cash for all periods presented.

In May 2016, the FASB issued ASU No. 2016-12*, Revenue from Contracts with Customers (Topic 606), Narrow-Scope Improvements and Practical Expedients*, or ASU 2016-12, which amends guidance in the new revenue standard, ASU No. 2014-09 *Revenue from Contracts with Customers (Topic 606)*, or ASU 2014-09, on collectability, noncash consideration, presentation of sales tax and transition. The amendments in ASU 2016-12 are effective for annual reporting periods beginning after December 15, 2017 (i.e., January 1, 2018), including interim periods within those reporting periods, which is the same as for ASU 2014-09, as amended by ASU No. 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date*, or ASU 2015-14. In April 2016, the FASB issued ASU No. 2016-10, *Revenue from Contracts with Customers (Topic 606), Identifying Performance Obligations and Licensing*, or ASU 2016-10*,* which clarifies the principle for determining whether a good or service is "separately identifiable" from other promises in the contract and, therefore, should be accounted for as a separate performance obligation. In that regard, ASU 2016-10 requires that an entity determine whether its promise is to transfer individual goods or services to the customer, or a combined item (or items) to which the individual goods and services are inputs. In addition, ASU 2016-10 categorizes intellectual property, or IP, into two categories: "functional" and "symbolic." Functional IP has significant standalone functionality. All other IP is considered symbolic IP. Revenue from licenses of functional IP is generally recognized at a point in time, while revenue from licenses of symbolic IP is recognized over time. ASU 2016-10 has the same effective date and transition requirements as ASU 2014-09, as amended by ASU 2015-14. In March 2016, the FASB issued ASU No. 2016-08, *Revenue from Contracts with Customers (Topic 606), Principal versus Agent Considerations (Reporting Revenue Gross versus Net)*, or ASU 2016-08, which clarifies the implementation guidance on principal versus agent considerations contained in ASU 2014-09 by specifying that the determination as to whether an entity that is involved in providing a good or a service to a customer is a principal or an agent is based upon whether the entity controls the good or the service before it is transferred to the customer. ASU 2016-08 has the same effective date and transition requirements as ASU 2014-09, as amended by ASU 2015-14. The adoption of these ASU's on January 1, 2018 did not have a material effect on the Company's financial position, results of operations or cash flows.

In January 2016, the FASB issued ASU No. 2016-01, *Financial Instruments—Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities.* The new guidance is intended to improve the recognition and measurement of financial instruments by requiring separate presentation of financial assets and financial liabilities by measurement category and form of financial asset (i.e., securities or loans and receivables) within the balance sheet or the accompanying notes to the financial statements, eliminating the requirement for public business entities to disclose the method(s) and significant assumptions used to estimate the fair value that is required to be disclosed for financial instruments measured at amortized cost within the balance sheet, requiring public business entities to use the exit price

notion when measuring the fair value of financial instruments for disclosure purposes, requiring equity investments (except those accounted for under the equity method of accounting, or those that result in consolidation of the investee) to be measured at fair value with changes in fair value recognized in net income, and requiring a reporting organization to present separately in other comprehensive income the portion of the total change in the fair value of a liability resulting from a change in the instrument-specific credit risk (also referred to as "own credit") when the organization has elected to measure the liability at fair value in accordance with the fair value option for financial instruments, among others. In February 2018, the FASB issued ASU No. 2018-03, *Technical Corrections and Improvements to Financial Instruments—Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities,* which is intended to clarify certain aspects of the guidance issued in ASU 2016-01. The Company adopted these standards effective January 1, 2018, which had no impact on the Company's consolidated financial statements.

Recent Accounting Pronouncements Not Yet Adopted

In November 2018, the FASB issued Accounting Standards Update No. 2018-18, Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606 ("ASU 2018-18"). The standard amends Accounting Standards Codification 808, Collaborative Agreements and Accounting Standards Codification 606, Revenue from Contracts with Customers, to clarify the interaction between collaborative arrangement participants that should be accounted for as revenue under ASC 606. In transactions when the collaborative arrangement participant is a customer in the context of a unit of account, revenue should be accounted for using the guidance in Topic 606. The amendments in Update No. 2018-18 are effective for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. The Company is currently evaluating the new guidance included in ASU 2018-18, but does not expect it to have a material impact on its consolidated financial statements.

In October 2016, the FASB issued ASU 2016-16, Income Taxes (Topic 740): *Intra-Entity Transfers of Assets Other than Inventory*, or ASU 2016-16 which requires that an entity recognize the income tax consequences of an intra-entity transfer of assets other than inventory when the transfer occurs. The guidance must be applied using the modified retrospective basis. The Company does not expect the provisions of ASU 2016-16 to have a material impact on its current financial statements. This update will be effective for the Company at the beginning of fiscal 2019.

In February 2016, the FASB issued ASU No. 2016-02, "Leases" (ASC 842). The amended guidance requires lessees to recognize lease liabilities and right-of-use assets on the balance sheet for all leases with terms longer than 12 months and provides enhanced disclosures on key information of leasing arrangements. In July 2018, further amendments were issued to clarify how to apply certain aspects of the amended lease guidance and to address certain implementation issues. The amended guidance is effective for us commencing in the first quarter of 2019. Early adoption is permitted. We plan to adopt the amended guidance on the effective date and expect to elect the package of practical expedients. We expect the adoption of the amended guidance will materially affect our consolidated balance sheet and that the primary impact will be recognition of minimum commitments at present value of our noncancelable operating leases as lease liabilities and corresponding right-of-use assets. In July 2018, the FASB issued ASU No. 2018-10, which provides narrow amendments to ASU No. 2016-02 to clarify how to apply the rate implicit in the lease, impairment of the net investment in the lease, lessee reassessment of lease classification, variable payments that depend on an index or rate and certain transition adjustments. In July 2018, the FASB also issued ASU No. 2018-11, which provides targeted improvements to ASU No. 2016-02 to provide entities the transition option to not apply the standard in the comparative periods presented in the year of adoption. The Company will adopt the new standard effective January 1, 2019 using the modified retrospective transition method using the practical expedients model and a discount rate in the range of 8% to 10%, and

elect to not apply the standard in the comparative periods presented in the year of adoption. We estimate that upon implementation, we will record a right-of-use asset between $3.3 million and $3.6 million and a corresponding liability between $3.6 million and $3.8 million. We are continuing to evaluate the impact that the amended lease guidance will have on our consolidated financial statements, systems, processes and internal controls.

3. Asset Acquisition:

On October 5, 2018, the Company entered into an agreement to acquire Vector Neurosciences Inc. ("Vector") pursuant to an Agreement and Plan of Merger (the "Merger Agreement") by and among the Company, Vector, VN Acquisition, Inc., a wholly-owned subsidiary of the Company ("Merger Sub 1"), VN Acquisition 2, Inc., a wholly-owned subsidiary of the Company ("Merger Sub 2"), the Vector stockholders named therein and the Vector stockholder representative, pursuant to which Merger Sub 1 was merged with and into Vector, with Vector being the surviving corporation ("Merger 1") and, immediately following Merger 1, Vector was merged with and into Merger Sub 2, with Merger Sub 2 being the surviving corporation (together with Merger 1, the "Merger"). As a result of the Merger, Vector is a wholly-owned subsidiary of the Company. The Company's board of directors, Vector's board of directors and Vector's stockholders have, in each case, unanimously approved the Merger, the Merger Agreement and the transactions contemplated by the Merger Agreement. The merger consideration to Vector's stockholders consists of 225,000 shares of the Company's Ordinary Shares as initial merger consideration, consisting of 202,500 shares which were issued at the closing of the Merger and an additional 22,500 shares to be issued 18 months following the closing, subject to any indemnification claims under the Merger Agreement (See Note 12).

In addition, pursuant to the terms of the Merger Agreement, the Company will issue to Vector's stockholders additional Ordinary Shares equal to a maximum value of $21,000,000 if specified regulatory milestones are met and will make royalty payments to Vector's stockholders in an amount equal to a percentage of the value of sales of certain products developed based on the Vector assets, which royalty payments are also payable in Ordinary Shares. The number of Ordinary Shares to be issued in connection with such milestones and royalties will be based on the three-day average closing price of the Company's Ordinary Shares immediately prior to the date of determination of the value of the payment.

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 $2,990,250 as of October 5, 2018. 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 additional alternative use of these assets. Additionally, under ASC 805, the Company determined that as of the acquisition date and as of December 31, 2018, the contingent milestone payments in the aggregate amount of $21,000,000, and royalty payments have not been resolved and therefore have not been recorded as liability.

4. Prepaid Expenses:

Prepaid expenses at December 31, 2018 and 2017 consist of the following:

	December 31, 2018	December 31, 2017
Insurance	$ 623,314	$ 163,284
Clinical Trial Costs	373,723	839,644
Research and Development	352,658	624,348
Other	330,233	160,595
Dues and License Fees	169,073	145,594
Rent	88,784	27,778
	$1,937,785	$1,961,243

5. Property, Plant and Equipment, net:

Property, plant and equipment, net at December 31, 2018 and 2017 consist of the following:

	December 31, 2018	December 31, 2017
Leasehold Improvements	$11,538,377	$10,873,895
Capitalized Leasehold Interest	7,150,611	—
Manufacturing Equipment	3,779,950	2,477,637
Laboratory Equipment	1,485,544	993,409
Computer and Office Equipment	334,525	276,100
Asset Retirement Obligation	113,678	153,133
Furniture & Fixtures	88,660	93,786
	24,491,345	14,867,960
Less: Accumulated depreciation	(2,477,108)	(612,231)
	$22,014,237	$14,255,729

In February 2016, the Company sublet a manufacturing facility for a term of 5 years, that included an additional 5-year option. This sub-lease was accounted for as an operating lease. On December 14, 2018, the Company executed a new sub-lease for this manufacturing facility whereby the sub landlords remaining term of 108 years was assigned to the Company. Under the new sub-lease, the Company paid a one-time fee of £5,250,000 (approximately $6,615,000 assuming a rate of $1.26 per GBP on the date of the acquisition) for the assignment and will no longer pay any base rent for the remaining 108 years. The one-time fee and related transaction costs, in the aggregate amount of £5,613,165 (approximately $7,150,611 using a rate of $1.2739 per GBP at December 31, 2018), have been accounted for as a capital lease and recorded as property, plant and equipment. The Company determined that the cost of the new sub-lease would be amortized on a straight-line basis over a 25-year estimated useful life.

In connection with the above-mentioned lease, the Company estimated that it had an asset retirement obligation at the end of the initial five-year lease term in the amount of $306,400. The Company discounted the asset retirement obligation using an 8% discount rate and recorded an asset retirement obligation in the amount of $205,659 as of December 31, 2016, which is included in leasehold improvements and was being depreciated over the five-year term of the lease (see Note 15). As of December 31, 2017, the Company determined that it was probable that it would exercise the additional five-year option provided for in the sub-lease. Therefore, the company remeasured the asset retirement obligation using the remaining eight-year new sub-lease term and recorded a reduction in the asset retirement obligation of $75,011 recorded in

leasehold improvements. On December 14, 2018, upon execution of the new sub-lease, the Company remeasured the asset retirement obligation using the remaining 25-year estimated useful life and recorded a reduction in the asset retirement obligation of $99,090 recorded in leasehold improvements.

In connection with two operating leases entered into in July 2018, the Company estimated that it had asset retirement obligations at the end of the eight-year terms in the amount of $140,129. The Company discount the asset retirement obligation using an 8% discount rate and recorded an asset retirement obligation in the aggregate amount of $69,286, which is included in leasehold improvements and is being depreciated over the eight-year term of the lease.

Capitalized leases in the amount of $95,880 are included in computer and office equipment at December 31, 2018 and 2017, and accumulated depreciation of $62,912 and 34,552 at December 31, 2018 and 2017, respectively.

A capitalized lease in the amount of $7,150,611 is included in capitalized leasehold interest at December 31, 2018 and accumulated depreciation of $6,928 at December 31, 2018.

Depreciation expense was $2,052,948 and $679,177 for the years ended December 31, 2018 and 2017 respectively.

6. Restricted Cash:

The Company is required to maintain a stand-by letter of credit as a security deposit under the ARE-East River Science Park LLC ("ARE") lease (see Note 15) through the end of the lease term in December 2021, plus three months. The fair value of the letter of credit approximates its contract value. The Company's bank requires the Company to maintain a restricted cash balance to serve as collateral for the letter of credit issued to the landlord by the bank. As of December 31, 2018 and 2017, the restricted cash balance for the ARE lease was invested in a commercial money market account.

The Company had $123,376 of restricted cash included in long-term assets as of December 31, 2018 and 2017 and is measured using level 1 inputs.

7. Accrued Expenses:

Accrued expenses at December 31, 2018 and 2017 were comprised of the following:

	December 31, 2018	December 31, 2017
Compensation and Benefits	$ 5,731,438	$2,386,903
Clinical Trial Costs	4,013,094	4,859,410
Professional Fees	914,540	231,923
Consulting	821,009	1,220,477
Research and Development	236,271	73,379
Rent	122,770	387,267
Interest	40,800	33,437
Other	111,775	140,148
	$11,991,697	$9,332,944

8. Capitalized Leases:

In 2015, the Company acquired certain office equipment in the amount of $17,817 under a 3-year lease arrangement. The Company determined that the lease should be capitalized since it contained a bargain

purchase option for the equipment at the end of the lease term. Total payments under the capital lease amounted to $20,502 and had an interest rate of 9.35%.

In 2017, the Company acquired additional office equipment in the amount of $78,063 under a 3-year lease arrangement. The Company determined that the lease should be capitalized since it contained a bargain purchase option for the equipment at the end of the lease term. Total payments under the capital lease will amount to $86,145 and has an interest rate of 6.90%.

In December 2018, the Company entered into a sub-lease for the remaining term of 108 years (see Note 5). The Company determined that the lease should be capitalized since the lease term exceeded 75% of the estimated 25-year useful life of the leasehold interest. The Company made a one-time upfront payment for the assignment of the lease and will not have any obligation to make future rent payments. The Company capitalized as property, plant and equipment, the initial one-time upfront payment and related transaction costs in the aggregate amount of $7,150,611.

The following is a schedule, by year, of future minimum lease payments under the capital leases together with the present value of the net minimum lease payments as of December 31, 2018:

2019	28,715
2020	7,179
Total minimum lease payments	35,894
Less: amount representing interest	(1,598)
Present value of net minimum lease payments	34,296
Less: current portion	(27,199)
Obligations under capital lease, less current portion	$ 7,097

9. Notes Payable

On October 26, 2017, in connection with an amendment and termination of a lease, the Company issued a promissory note in the amount of $1,442,009 to ARE, the landlord and also a related party (see Note 15). The note bears interest at the rate of 5% per annum and was due on December 31, 2018. However, if the Company had sufficient liquidity, as defined in the note, then the note, including accrued interest, would become due and payable at that time. In accordance with the sufficient liquidity provision, the Company repaid the note, plus accrued interest, in the amount of $1,472,433 during the three-month period ended March 31, 2018. The Company recorded interest expense in the consolidated statements of operations and comprehensive loss in connection with the note in the amount of $17,386 and $13,037 for the years ended December 31, 2018 and 2017, respectively.

10. Collaboration Agreement

On October 16, 2018, the Company entered into a research collaboration agreement with Janssen Pharmaceuticals, Inc., (“Janssen”), to develop regulatable gene therapy treatment using the Company’s proprietary riboswitch technology. As part of the agreement, the Company will use its proprietary riboswitch technology to engineer regulatable gene therapy constructs encoding proprietary gene sequences from Janssen.

Upon execution of the agreement, Janssen paid the stage 1 fee in the amount of $658,667 and such payment was recorded as deferred research funding. The stage 1 fee is being amortized over the estimated research term of eight months. During the year ended December 31, 2018, the Company amortized $224,576 of the deferred research funding, which was recorded as an offset to research and development expenses. Deferred research funding in the amount of $434,091 is included as other current liabilities on the consolidated balance sheet at December 31, 2018.

11. Share-Based Compensation

2018 and 2016 Equity Incentive Plans

The Company's 2018 Incentive Award Plan and 2016 Equity Incentive Plan (the "Plans"), were adopted by the Company's board of directors and shareholders. Under the Plans, the Company has granted share options to selected officers, employees and non-employee consultants. The Company's board of directors administer the Plans. Options granted under the Plans have a maximum contractual term of ten years. Options granted generally vest 25% on the first anniversary date of grant and the balance ratably over the next 36 months. Options granted to directors generally vest on the first anniversary date of grant. Upon the adoption of the 2018 Incentive Award Plan, the Company ceased issuing awards under the 2016 Equity Incentive Plan.

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, 2018 and 2017 is as follows:

STOCK OPTION TABLE

	Number of Options	Weighted-Average Exercise Price	Aggregate Instrinsic Value
Outstanding at December 31, 2016	333,660	$ 7.72	
Granted	611,933	3.73	
Exercised	(1,288)	(7.57)	
Expired	—	—	
Forfeited	(5,668)	(7.72)	
Outstanding at December 31, 2017	938,637	$ 5.12	
Granted	2,334,285	8.63	
Exercised	—	—	
Expired	—	—	
Forfeited	(10,557)	(5.51)	
Outstanding at December 31, 2018	3,262,365	$ 7.64	$6,903,313
Weighted average remaining contractual life of options outstanding as of December 31, 2017 (yrs)	9.09		
Weighted average remaining contractual life of options outstanding as of December 31, 2018 (yrs)	9.24		
Options exercisable at December 31, 2017	186,394	$ 7.72	
Options exercisable at December 31, 2018	535,241	$ 5.79	
Weighted average remaining contractual life of options exercisable as of December 31, 2017 (yrs)	8.21		
Weighted average remaining contractual life of options exercisable as of December 31, 2018 (yrs)	7.88		

The total fair value of options vested during the years ended December 31, 2018 and 2017 was $1,387,607 and $898,699, respectively.

During the years ended December 31, 2018 and 2017, the Company granted 2,334,285 and 611,933 share options, respectively. The grant date fair values of the stock options granted were estimated using the Black-Scholes option valuation model with the following ranges of assumptions (see Note 2):

	2018	2017
Risk-free interest rate	2.32% - 2.98%	2.28% - 2.51%
Expected volatility	90%	80%
Expected dividend yield	0%	0%
Expected life (in years)	5.5 - 10.0	5.5 - 10.0

As of December 31, 2018 and 2017, the total compensation expense relating to unvested options granted that had not yet been recognized was $17,415,098 and $987,413, respectively which is expected to be realized over a period of 4.0 and 3.42 years, respectively. The Company will issue shares upon exercise of options from Ordinary Shares reserved.

The weighted average grant date fair value of options granted during the years ended December 31, 2018 and 2017 was $6.53 and $3.10, respectively.

Restricted Ordinary Shares

In 2015, in connection with certain service and consulting agreements, certain employees and a consultant were awarded an aggregate of 867,935 restricted Ordinary Shares of the Company. Such shares were subject to forfeiture over a three-year service period. The shares granted to the consultant and employees were valued at $7.72 and $7.76 per share, respectively, and were included in loss from operations over the requisite service period. As of December 31, 2018, all such shares are no longer subject to forfeiture as the three-year service period has been completed.

On June 7, 2018, 1,306,348 restricted Ordinary Shares, which represented 5% of the fully-diluted outstanding shares of the Company as of such date, were issued to certain members of senior management in accordance with their employment agreements. One-third of such shares vested immediately, with the balance vesting quarterly over the next eight quarters beginning three months after the effectiveness of the Company's registration statement on Form S-1 filed with the SEC on June 7, 2018 (the "Registration Statement"). The shares were valued at $15.00 per share and the related share-based compensation expense, which is recognized over the requisite service period, is included in general and administrative expenses in the consolidated statements of operations and comprehensive loss. Additionally, under the terms of the employment agreements, the Company was required to pay the income taxes incurred by the grantees in connection with the grant of those restricted shares. Total compensation expense in connection with the issuance of those restricted Ordinary Shares, in the amount of $20,141,876, of which $10,156,868 was share-based, was recorded as general and administrative expense during the year ended December 31, 2018 (See Note 16).

A summary of the restricted Ordinary Shares is as follows:

	Ordinary Shares	$ Value
Non-vested at December 31, 2016	386,608	$ 3,020,191
Vesting during 2017	(280,695)	(2,154,330)
Non-vested at December 31, 2017	105,913	865,861
Issued during 2018	1,306,348	19,595,220
Vesting during 2018	(759,087)	(10,663,471)
Non-vested at December 31, 2018	653,174	$ 9,797,610

Ordinary Shares

On March 1, 2018, a funding milestone was met under the employment agreements for certain members of senior management. Accordingly, the employees were issued an aggregate of 550,162 fully vested Ordinary Shares, which represented 3% of the fully-diluted outstanding shares of the Company as of such date. The shares were recorded as share-based compensation in the amount of $3,096,104. Additionally, under the terms of the employment agreements, the Company was required to pay the income taxes incurred by the grantees in connection with the grant of those shares. Total compensation expense in connection with the issuance of those Ordinary Shares, in the amount of $6,456,215, of which $3,096,104 was share-based, was recorded as general and administrative expense during the year ended December 31, 2018.

During the years ended December 31, 2018 and 2017 the Company recognized total share-based compensation expense in the accompanying consolidated statements of operations and comprehensive loss as follows:

	2018	2017
Research and development	$ 3,372,054	$2,374,899
General and administrative	14,511,500	584,832
Total share based compensation	$17,883,554	$2,959,731

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, 2018 and 2017.

12. Ordinary Shares, Convertible Preferred C Shares and Shareholders' Deficit:

Ordinary Share Issuances

2018

As discussed in Note 11, on March 1, 2018, a funding milestone was met under the employment agreements for certain members of senior management. Accordingly, the employees were issued an aggregate of 550,162 fully vested Ordinary Shares.

In connection with the Company's initial public offering, on June 7, 2018, the Company issued 5,000,000 Ordinary Shares at an offering price of $15.00 per share for gross proceeds of $75,000,000, excluding offering costs of $9,807,622.

Also, as discussed in Note 11, on June 7, 2018, upon the effectiveness of the Company's Registration Statement, 1,306,348 restricted Ordinary Shares, which represented 5% of the fully-diluted outstanding shares of the Company as of such date, were issued to certain members of senior management in accordance with their employment agreements. One-third of such shares vested immediately, with the balance vesting quarterly over the next eight quarters.

On October 5, 2018, in connection with an acquisition, the Company issued 202,500 Ordinary Shares with an additional 22,500 shares to be issued 18 months following the closing, subject to any indemnification claims under the merger agreement.

2017

On July 31, 2017, the Company issued 1,288 Ordinary Shares in connection with the exercise of an option.

On August 16, 2017, the Company issued 6,441 Ordinary Shares in connection with a research agreement.

Convertible Preferred C Shares

Issuances

2018

During the year ended December 31, 2018, the Company issued 5,425,124 Preferred Shares at an offering price of approximately $10.48 per share for gross proceeds of $56,849,611, excluding offering costs of $690,473.

Also, during the year ended December 31, 2018, the Company issued 129,419 Preferred Shares in lieu of payment of accounts payable in the aggregate amount $1,355,097 to certain vendors.

On March 15, 2018, the Company issued 13,360 Preferred Shares in connection with a license agreement.

On June 7, 2018, upon effectiveness of the Company's Registration Statement on Form S-1, all of the 11,501,432 outstanding Preferred Shares were automatically converted into 11,501,432 Ordinary Shares. In connection with the conversion of the Preferred Shares, $664,718 of unaccredited financing costs were fully accreted.

2017

During the year ended December 31, 2017, the Company issued 9,739 Preferred Shares at an offering price of $20.96 per share and 1,598,418 Preferred Shares at an offering price of $10.48 per share for gross proceeds of $16,854,656, excluding offering costs of $98,804. The net proceeds of the offering were used for working capital, research and development and general corporate purposes.

On November 2, 2017, a note payable to a related party in the amount of $2,500,000 was converted at the rate of $10.48 per share, into 238,579 Preferred Shares (see Note 15).

Warrants

In connection with the issuance of 715,737 Preferred Shares on September 21, 2017, at an offering price of $10.48 per share, the Company issued warrants to purchase 695,696 Preferred Shares at an exercise price of $10.48 per share. The warrants expired on the first of the following to occur:

(i) an Asset Sale;

(ii) a Qualified IPO;

(iii) a Share Sale;

(iv) the winding up of the Company; or

(v) On the third anniversary of the date of issuance

The Black-Sholes value of the warrants in the amount of $1,660,500 was accounted for as a warrant liability and a discount to the Preferred Shares at the time of issuance and were being accreted over the expected term of the Preferred Shares (see Note 2).

The Black-Scholes value of the warrants in the amount of $553,500 was recorded as a warrant liability and charged to convertible note inducement expense within the statement operations and comprehensive loss at the time of issuance.

Both of the warrants were revalued under the Black-Scholes valuation model at December 31, 2017, which resulted in an increase of the warrant liability in the amount of $465,633, which was charged to change in fair value of warrant liability within the statement of operations and comprehensive loss.

The warrant liability at December 31, 2017 was $2,679,633.

On June 5, 2018, all of the outstanding warrants to purchase 927,594 Preferred Shares at an exercise price of approximately $10.48 per share were exercised for aggregate cash proceeds of $9,720,000.

13. Net Loss per Share

The Company computes net loss per share in accordance with ASC 260-10, *Earnings per Share* (see Note 2).

Basic and diluted net loss per share is computed as follows:

	2018	2017
Net loss—basic and diluted	$(82,865,874)	$(31,044,535)
Accretion of Preferred Shares financing costs	(1,806,512)	(191,963)
Accretion of warrant	—	(615,000)
Adjusted net loss—basic and diluted	$(84,672,386)	$(31,851,498)
Weighted-average ordinary shares outstanding:		
Basic and Diluted	18,948,520	8,572,315
Net loss per share:		
Basic and Diluted	$ (4.47)	$ (3.72)

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, 2018	December 31, 2017
Preferred Shares	—	5,005,934
Restricted Ordinary Shares subject to forfeiture	653,174	105,913
Stock options	3,262,365	938,637
Warrants	—	927,594
	3,915,539	6,978,078

14. Income Taxes:

Since the Company has recurring losses and a valuation allowance against deferred tax assets, there is no tax expense (benefit) for the year ended 2017. For the year ended December 31, 2018, the Company recognized a tax benefit of $(474,391).

The subsidiaries each file separate tax returns in their respective tax jurisdictions.

As of December 31, 2018, the Company had federal and state net operating loss ("NOL") carryforwards in the United States of approximately $14,210,000 and $14,155,000, respectively, and in the United Kingdom of approximately $94,100,000, which are available to reduce future taxable income. The U.S. federal and state NOL carry forwards incurred prior to January 1, 2018 in the amount of approximately $6.8 million and $6.7 million, respectively, will begin to expire in 2036. The U.S. NOL incurred after December 31, 2018 and the U.K. NOL will be indefinitely carried forward. Also, as of December 31, 2018, the Company had orphan drug and research and development credits in the U.S. in the amount of $1,134,000 which will begin to expire in 2036. The NOL carry forwards are subject to review and possible adjustment by the U.S., U.K. and state tax authorities. NOL carry forwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders, as defined under

Sections 382 Internal Revenue Code, as well as CTA 2010 Part 14 under the UK tax rules. This could limit the amount of NOLs that the Company can utilize annually to offset future taxable income or tax liabilities. As of December 31, 2018, the Company has performed such an analysis and determined that there were no limitations in the U.K. However, for U.S. purposes the Company determined that a change of ownership occurred in April 2016. The Company is still in the process of determining the annual limitation on losses that occurred prior to April 2016. Subsequent ownership changes and proposed future changes to the UK (or US) tax rules in respect of the utilization of losses carried forward may further affect the limitation in future years, if any. Additionally, the Company has not undertaken a study on the completeness of the U.S. orphan drug and research and development credit.

The Company's pre tax earnings from the United Kingdom and United States locations are as follows:

	December 31, 2018	December 31, 2017
United Kingdom	$(73,359,977)	$(26,458,625)
United States	(9,980,287)	(4,585,910)
	$(83,340,264)	$(31,044,535)

The Company is subject to the corporate tax rate in the U.K. as a Limited U.K. corporation.

The following table summarizes a reconciliation of income tax benefit compared with the amounts at the U.K. statutory income tax rate:

	December 31, 2018		December 31, 2017	
Statutory rate	(15,834,650)	19.00%	(5,976,073)	19.25%
Permanent differences—other	1,438,934	-1.73%	654,648	-2.11%
RTP and other adjustments	387,509	-0.46%	(152,948)	0.49%
U.K. tax credit	1,707,489	-2.05%	539,136	-1.74%
U.S. tax credit	(436,250)	0.52%	(363,665)	1.17%
Foreign tax rate differential	(171,693)	0.21%	(673,619)	2.17%
State and local rate, net of federal tax	(1,159,522)	1.39%	(446,683)	1.44%
UK Rate Change (17% at expected DTA turn)	1,104,863	-1.33%	482,351	-1.55%
U.S. state rate change	(6,496)	0.01%	993,998	-3.20%
Change in valuation allowance	12,495,426	-14.99%	4,942,855	-15.92%
Actual income tax benefit effective tax rate	(474,391)	0.57%	—	0.00%

The Expense/(Benefit) for income taxes from continuing operations consists of the following:

	December 31, 2018	December 31, 2017
Current Tax Expense/(Benefit)		
United Kingdom	—	—
United States	—	—
Total Current	—	—
Deferred Tax Expense/(Benefit)		
United Kingdom	$ (8,888,096)	$(3,759,109)
United States	(3,606,275)	(1,183,746)
Total Deferred	(12,494,371)	(4,942,855)
Change in Valuation Allowance	12,019,880	4,942,855
Total Income Tax Expense/(Benefit)	$ (474,391)	$ —

Income tax (benefit) expense for each year is allocated to continuing operations, discontinued operations, extraordinary items, other comprehensive income, the cumulative effects of accounting changes, and other charges or credits recorded directly to shareholders' equity. *ASC 740-20-45 Income Taxes, Intraperiod Tax Allocation, Other Presentation Matters* includes an exception to the general principle of intraperiod tax allocations. The codification source states that the tax effect of pretax income or loss from continuing operations generally should be determined by a computation that considers only the tax effects of items that are included in continuing operations. The exception to that incremental approach is that all items (i.e. other comprehensive income, discontinued operations, etc.) be considered in determining the amount of tax benefit that results from a loss from continuing operations and that benefit should be allocated to continuing operations. That is, when a company has a current period loss from continuing operations, management must consider income recorded in other categories in determining the tax benefit that is allocated to continuing operations. This includes situations in which a company has recorded a full valuation allowance at the beginning and end of the period, and the overall tax provision for the year is zero. The intraperiod tax allocation is performed once the overall tax provision has been computed and allocates that provision to various income statement (continuing operations, discontinued operations), other comprehensive income and balance sheet captions. While the intraperiod tax allocation does not change the overall tax provision, it results in a gross-up of the individual components. The level of application has been applied on the group level.

As the Company experienced a net loss from operations for the year ended December 31, 2018 and other comprehensive income from foreign currency translation adjustments, the Company has allocated income tax expense against the components of other comprehensive income in 2018 using a 17% effective tax rate. Income tax benefit for the year ended December 31, 2018 includes a benefit of $(474,391) due to the required intraperiod tax allocation. Conversely, other comprehensive income for the year ended December 31, 2018 includes income tax expense of $474,391.

Deferred Tax Assets/(Liabilities)

	December 31, 2018		
	Total	UK	US
Deferred Tax Assets:			
Net operating loss carryforwards	$ 20,646,185	$ 16,000,329	$ 4,645,856
Other	1,414,690	(46,604)	1,461,294
Tax Credit	1,133,656	—	1,133,656
Deferred tax assets	23,194,531	15,953,725	7,240,806
Less: valuation allowance	(23,194,531)	(15,953,725)	(7,240,806)
Net deferred tax asset	$ —	$ —	$ —

	December 31, 2017		
	Total	UK	US
Deferred Tax Assets:			
Net operating loss carryforwards	$ 9,462,690	$ 6,909,754	$ 2,552,937
Other	539,008	152,554	386,454
Tax Credit	697,406	—	697,406
Deferred tax assets	10,699,105	7,062,308	3,636,797
Less: valuation allowance	(10,699,105)	(7,062,308)	(3,636,797)
Net deferred tax asset	$ —	$ —	$ —

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 against its deferred tax assets at December 31, 2018 and 2017 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 U.K. and U.S. corporation tax rates have been announced which will impact future accounting periods. In his budget of July 8, 2015, the Chancellor of the Exchequer announced a reduction in the U.K. corporation tax rate to 19% for the financial year beginning April 1, 2017 and a further reduction to 18% for the financial year beginning April 1, 2020. These changes received Royal Assent on November 18, 2015. The U.K. Finance Act 2016 provides for a further reduction in the corporation tax rate to 17% for the Financial Year beginning April 1, 2020. This change was enacted on September 15, 2016. As the Company does not expect to be able to utilize its NOL's in the U.K. prior to its financial year beginning on January 1, 2021, if at all, the deferred tax has been calculated using a tax rate of 17%.

In the United States, the corporation tax rate was reduced to 21% for the financial year beginning January 1, 2018. As these changes were enacted prior to the December 31, 2017 balance sheet date, deferred tax has been calculated accordingly in these consolidated financial statements, which represented a decrease in the prior years deferred tax assets of approximately $994,000.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2018 and 2017, 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, United Kingdom and the Netherlands, and various state jurisdictions. For the US, the statute of examination is open for tax years 2015, 2016, 2017 and 2018. For the UK and the Netherlands, the statute of examination is open for tax years 2017 and 2018.

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.

15. Related Party Transactions:

Transition Services Agreement

Effective April 24, 2015, the Company entered into a transition services agreement (the "TSA") with Kadmon, which owned 12.9% of the Company at December 31, 2018, whereby Kadmon would provide office and laboratory facilities as well as certain other personnel support activities to the Company. Under the agreement, the Company is charged for (i) rent based upon the square footage of the office and laboratory facilities used by the Company (ii) other personnel support activities based upon the hours of the personnel providing the support activities, and (iii) and other direct costs incurred by Kadmon on behalf of the Company, plus a 7% administrative fee. The TSA terminated on April 24, 2018 and the Company is currently leasing office space on a month to month basis from Kadmon.

During the years ended December 31, 2018 and 2017, the Company incurred the following charges in connection with the TSA which are included in loss from operations:

	2018	2017
Rent	$557,698	$548,229
Personnel	6,493	39,721
Other	6,334	5,983
Total charges incurred	$570,525	$593,933

During the year ended December 31, 2018 and 2017, the Company made cash payments totaling $1,431,555 and $275,941, respectively.

The amount due to Kadmon at December 31, 2018 and 2017 is $0 and $861,030, respectively, and is disclosed as Due to Kadmon on the Company's consolidated balance sheets.

Research Agreement

Effective October 23, 2016, the Company entered into a four-year master services agreement with UCL Consultants Limited, an entity affiliated with University College of London ("UCL"), which is a shareholder of the Company. Pursuant to the agreement, UCL Consultants Limited provides pre-clinical research and development under the direction of the Company. In connection with the agreement, the Company issued several work orders during the years ended December 31, 2016 and 2017 in the aggregate amounts of £1,402,202, or approximately $1,885,000, based upon the average exchange rates during the years ended December 31, 2016 and 2017, respectively. Either party may terminate the agreement by giving 30 days written notice. Total research and development expenses under this agreement for the years ended December 31, 2018 and 2017 was approximately $636,000 and $538,000, respectively. Future obligations under the agreement equal £612,382, or approximately $779,685, through October 2020.

The amount due to UCL under the master services agreement at December 31, 2018 and 2017 is $389,101 and $775,315, respectively and is included in accounts payable and accrued expenses on the Company's consolidated balance sheets.

Effective September 1, 2016, the Company entered into a manufacturing and drug supply agreement with UCL. Pursuant to the agreement, UCL manufactured materials for the Company's clinical trials under the

direction of the Company. The agreement was terminated in January 2018. Total research and development expenses under this agreement for the years ended December 31, 2018 and 2017 was approximately $0 and $1,904,352, respectively.

The amount due to UCL under the manufacturing and drug supply agreement at December 31, 2018 and 2017 is $0 and $2,466,142, respectively and is included in accrued expenses on the balance sheet.

Leases

July 2016 Lease

Effective July 1, 2016, the Company entered into a non-cancellable operating lease for laboratory and related office facilities in New York with ARE, an entity that is under common control by an entity that is a minority shareholder of the Company and whose executive chairman and founder is a director of the Company. The lease provides for monthly base rent and property management fees, including rent escalations and rent holidays, plus operating expenses during the lease term, which expires on December 31, 2021. The Company records monthly rent expense on a straight-line basis from July 1, 2016 through December 31, 2021. As of December 31, 2018 and 2017, the balance of deferred rent, representing the difference between cash rent paid and straight-line rent expense, was $201,264 and $231,276, respectively.

Total rent expense under this operating lease was $487,555 and $487,559 for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018, the aggregate future minimum rental payments under this lease are $1,663,952.

In connection with the signing of this lease, the Company entered into a standby letter of credit agreement for $122,866, which serves as a security deposit for the premises. The standby letter of credit expired on July 7, 2017 and was automatically renewed annually through July 7, 2021. This standby letter of credit is secured with restricted cash in a money market account (see Note 6).

December 2016 Lease

Effective December 15, 2016, the Company entered into another non-cancellable operating lease with ARE, expiring on October 31, 2032, for laboratory and office facilities in New York. The lease provided for monthly base rent, including rent escalations, property management fees and rent holidays, plus operating expenses during the lease term. The Company recorded monthly rent expense on a straight-line basis from December 15, 2016 through October 31, 2032. On October 26, 2017, the lease was amended, whereby the lease would terminate on March 31, 2018 and only base rent and management fees in the aggregate amount of $563,507 would be due from November 1, 2017 through March 31, 2018. Under the amendment, the Company issued a note to ARE in the amount of $1,442,009 (see Note 9), removed the balance of the deferred rent and accrued the future rent payments, all of which were recorded as rent expense at the time of the amendment, in accordance with ASC 420, Exit and Disposal Activities, as the Company had a cease use date as of the date of the amendment.

Total rent expense under this operating lease was $0 and $1,660,806 for the years ended December 31, 2018 and 2017, respectively.

Convertible Note Payable

On May 1, 2017, the Company issued a convertible note in the amount of $2,500,000 to ARE. The note had an interest rate of 10% per annum and was convertible into Preferred Shares at any time at the option of the holder or would automatically convert into Preferred Shares in the event of an equity investment by a

mutually agreed upon institutional investor at a price per share equal to the lowest price paid per share by a purchaser of the Company's Preferred Shares. On November 2, 2017 the note was converted to 238,579 Preferred Shares at $2.70 per share. In accordance with the terms of the convertible note, the accrued interest in the amount of $145,833 was cancelled.

As an inducement to convert the convertible note, the Company issued a warrant to purchase 900,000 Preferred Shares, at an exercise price of $2.70 per share, to the holder of the convertible note, which was expenses in accordance with ASC 470 (see Note 12).

16. Commitments:

Operating Leases

In February 2016, the Company entered into a non-cancellable operating lease, expiring in February 2021, for manufacturing and office facilities in London, UK. The lease provides for an additional five-year term at the Company's option. The lease provides for monthly base rent, plus operating expenses and real estate taxes during the lease term.

Total rent expense under this operating lease was $273,430 and $279,303 for the years ended December 31, 2018 and 2017, respectively.

On October 1, 2017, the Company entered into a one-year non-cancellable operating lease, expiring in September 2018, for office and laboratory facilities in Leiden, Netherlands. The lease provides for monthly base rent plus operating expenses during the lease term. The lease provides for successive one-year extensions up to a maximum of four extensions. Total rent expense under this operating lease was $9,313 and $5,273 for the years ended December 31, 2018 and 2017, respectively.

In June 2017, the Company entered into two non-cancellable operating leases, expiring in July 2018, for office and laboratory facilities in London, UK. The lease provides for monthly base rent, rent holidays plus operating expenses and real estate taxes during the lease term. The Company records monthly rent expense on a straight-line basis from June 1, 2017 through July 23, 2018. As of December 31, 2018, the balance of deferred lease obligation, representing the difference between cash rent paid and straight-line rent expense, was $0. Total rent expense under theses operating leases was $73,846 and $85,222 for the years ended December 31, 2018 and 2017, respectively.

On July 27, 2018 the two leases for office and laboratory facilities in London, UK expired. Effective July 27, 2018, the Company entered into two new non-cancellable operating leases for the same office and laboratory facilities in London. The leases provide for annual base rent in the aggregate amount of approximately $363,000, plus operating expenses, through May 31, 2022, at which time the annual base rent will be revalued based on market rates at that time. The leases expire on May 24, 2027. Total rent expense under these operating leases was $148,561 and $0 for the years ended December 31, 2018 and 2017, respectively.

The aggregate future minimum rental payments under these operating leases are as follows:

2019	$ 353,782
2020	$ 350,284
2021	$ 350,284
2022	$ 350,284
2023	$ 350,284
Thereafter	$1,196,805
Total future rent payments	$2,951,723

The aggregate future minimum rental payments of all leases, including those discussed in Note 15 are as follows:

2019	$ 889,465
2020	$ 904,716
2021	$ 924,121
2022	$ 350,284
2023	$ 350,284
Thereafter	$1,196,805
Total future rent payments	$4,615,675

Service Agreements

On April 27, 2015, the Company entered into service agreements with a senior officer and a greater than 5% shareholder of the Company. Under the terms of the agreements, the employees will receive aggregate compensation of £300,000, which has been increased to a maximum aggregate amount of £410,000 per annum, or approximately $522,000 using exchange rates as of December 31, 2018. The agreements also provide for contributions to a defined contribution pension plan to be set up by the Company and a discretionary bonus. The agreements may be terminated at any time by either party by giving twelve-months' notice, or the Company may terminate the officer's employment effective immediately upon notice, and within 28 days making payment in lieu of notice consisting of a sum equivalent to the officer's annual salary for the relevant period. For the years ended December 31, 2018 and 2017, the Company recorded £1,001,000 and £724,000 or approximately $1,334,000 and $933,000, respectively, using the average exchange rates during the years ended December 31, 2018 and 2017, respectively, in research and development costs under these agreements. Future obligations to be paid under these agreements equal £150,333, or approximately $192,000, using exchange rates as of December 31, 2018.

In connection with the service agreements, on April 24, 2015, the employees were awarded, under a share award agreement (the "Share Award Agreement"), an aggregate of 2,704,800 restricted Ordinary Shares and 750 B ordinary shares, which B ordinary shares have been converted into Ordinary Shares, of the Company. Under the Share Award Agreement, such shares are subject to forfeiture ratably over a period of three years if the employee's do not remain an employee or consultant to the Company. The shares were valued at $7.76 per share and, in accordance with ASC 718, were charged to operations as share-based compensation ratably over the forfeiture period.

Employment Agreements

In February 2016, the Company entered into three-year employment agreements with certain senior officers of the Company. Under the terms of the agreements, which automatically renew for successive one-year terms, the employees will receive annual compensation in the aggregate amount of $710,000, which has been increased to a maximum aggregate amount of $1,075,000. The employment agreements also provide for an annual guaranteed cash bonus targeted at 100% of annual compensation. The agreements also provide for discretionary annual performance bonuses targeted to be not less than 50-60% of the employee's base salary and grants of restricted stock. In January 2018 the Company's compensation committee approved a discretionary bonus in the aggregate amount of $1,196,000. This discretionary bonus and the guaranteed bonus for 2017, in the amount of $850,000, were subject to compensation committee approval and meeting certain future funding conditions. On February 28, 2018, the funding conditions were met. The senior officers were granted their guaranteed and discretionary bonuses for the year ended December 31, 2018, in the aggregate amount of $3,415,000, which was paid in January 2019.

Additionally, the agreements provided for equity incentives of up to an aggregate maximum of 8.0% of the Company's fully diluted outstanding shares upon the attainment of certain milestones. On March 1, 2018, a funding milestone was met. Accordingly, the employees were issued an aggregate of 3% of the fully-diluted outstanding shares of the Company as of such date. On June 7, 2018, an additional milestone was met. Accordingly, the employees were issued an aggregate of 5% of the fully-diluted outstanding shares of the Company as of such date (see Note 11).

The employees are also entitled to participate in all incentive and deferred compensation and employee benefit programs available to employees and executive officers of the Company. Future obligations to be paid under these agreements equal $1,258,750, as of December 31, 2018.

Consulting and other Agreements

Effective September 28, 2015, the Company entered into a three-year consulting agreement with a consultant to provide ongoing strategic advice and to serve on the Company's board of directors. In connection with the agreement, the Company issued 662,910 restricted Ordinary Shares. Under the consulting agreement, such shares were subject to forfeiture ratably over a period of three years if the consultant does not remain a consultant to the Company. The shares were valued at $7.72 per share and were charged to general and administrative expenses upon the expiration of each forfeiture period. For the years ended December 31, 2018 and 2017, the Company recorded $263,970 and $351,960, respectively, in general and administrative expense under this agreement. There are no future obligations to be paid under the agreement.

Research Agreements

On April 24, 2015, the Company entered into a cooperative research and development agreement (CRADA) with the U.S. Department of Health & Human Services, as represented by the National Institute of Dental and Craniofacial Research (NIDCR) and Institute or Center of the National Institutes of Health (NIH). The CRADA provided for quarterly payments of $21,250 for three years through April 30, 2017 and a cost per patient for each patient enrolled in the Company's xerostomia clinical trial. The CRADA was amended on March 25, 2016 to extend the term through March 25, 2021 and to extend the annual payments throughout the revised term. Research and development expenses under the CRADA for the years ended December 31, 2018 and 2017 were $111,938 and $115,374, respectively. Future obligations to be paid under the CRADA, as amended, through March 25, 2021 equal $191,250.

On March 22, 2016, the Company entered into another CRADA with the NIDCR and NIH for the treatment of *Sjögren's syndrome* associated salivary hypofunction. The CRADA provides for quarterly payments of $104,500 for the first three years of the agreement plus a cost per patient for each patient enrolled in a clinical trial. The costs associated with years four and five of the *Sjögren's syndrome* CRADA will be determined at a later date. Total research and development expenses under this agreement for each of the years ended December 31, 2018 and 2017 were $418,000. There are no future obligations to be paid under the agreement.

Effective December 5, 2016, the Company entered into a three-year research collaboration agreement with Cornell University. Pursuant to the agreement, Cornell University provides research and development under the direction of the Company. In connection with the agreement, in July 2017, the Company issued 25,000 Ordinary Shares to Cornell University, which were recorded as research and development expenses in the amount of $17,000. The Company amended this agreement, effective June 12, 2017, to add a second three-year research collaboration project through September 2019. The Company further amended this agreement, effective October 18, 2018 to include additional costs related to the research. Total research and

development expenses under this agreement, as amended, for the years ended December 31, 2018 and 2017 were $1,625,152 and $1,029,904, respectively. Future obligations to be paid under the agreement through December 5, 2019 equal $2,002,228.

On February 14, 2017, the Company entered into a one-year research collaboration agreement with Cornell University in the amount of $679,473. On August 24, 2017, the agreement was amended to add an additional study in the amount of $182,520. Total research and development expenses under this agreement for the years ended December 31, 2018 and 2017 were $143,073 and $698,307, respectively.

License Agreements

Effective February 4, 2015, the Company entered into an exclusive worldwide license agreement with UCL Business, PLC ("UCL Business") to develop up to eight programs using certain ocular gene therapy technology. Under the terms of the agreement, as amended, the Company will pay UCL Business certain sales milestone payments, if achieved, in the aggregate amount of £39.8 million, or approximately $50.7 million using the exchange rate at December 31, 2018, and royalties on net sales, as defined upon commercialization. Additionally, the Company is responsible for all patent prosecution and maintenance costs incurred and will also pay UCL Business an annual maintenance fee of £50,000, or approximately $64,000, until the first commercial sale of a product. The agreement will terminate upon the later of (i) the last valid claim in a relevant product, (ii) the expiration of regulatory exclusivity to all licensed products, or (iii) the 10th anniversary of the first commercial sale of a product. Total research and development expenses under the agreement for the years ended December 31, 2018 and 2017 were $75,073 and $73,250, respectively.

Effective July 28, 2017, the Company entered into another exclusive worldwide license agreement with UCL Business for an additional program using certain ocular gene therapy technology. The Company will pay UCL Business certain milestone payments, royalties and annual maintenance fees under the same terms and conditions as the license dated February 4, 2015. Total research and development expenses under the agreement for the years ended December 31, 2018 and 2017 were $66,630 and $82,260, respectively.

Effective March 15, 2018, the Company entered into another exclusive worldwide license agreement with UCL Business for an additional program using certain ocular gene therapy technology. The Company will pay UCL Business certain milestone payments, royalties and annual maintenance fees under the same terms and conditions as the license dated February 4, 2015. Total research and development expenses under the agreement for the years ended December 31, 2018 and 2017 were $133,728 and $0, respectively.

On September 7, 2018, the Company entered into an exclusive licensing agreement with the National Institutes of Health for worldwide rights to expanded indications for use of AAV-AQP1 for treatment of xerostomia (dry mouth) and xerophthalmia (dry eye) associated with *Sjögren's syndrome.* This agreement expands the Company's original exclusive licensing agreement with the NIH for exclusive worldwide rights to AAV-AQP1 that was executed as of November 9, 2017. AAV-AQP1 is currently in Phase 1/2 development for treatment of grade 2 or 3 radiation-induced xerostomia. Total research and development expenses under the agreement for the years ended December 31, 2018 and 2017 were $50,000 and $0, respectively.

Effective January 1, 2016, the Company entered into an Agreement ("Agreement") and Plan of Merger to acquire all of the outstanding shares of BRI-Alzan from the shareholders of BRI-Alzan. In connection with the Agreement, the Company will pay certain development milestone payments if achieved, in the aggregate amount of $4.5 million, and annual royalty payments on annual net sales following the first commercial sale of any product containing the technology acquired. Total research and development expenses under the agreement for the years ended December 31, 2018 and 2017 were $15,000 and $30,000, respectively.

17. 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 HM Revenue and Customs (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 not required to contribute, but may make optional contributions up to the annual allowance HMRC limits.

Under the HMRC requirements, current required 6+minimum employer contributions are 5-6% but will rise to 8-9% after April 2019.

During the years ended December 31, 2018 and 2017, employer contributions to all plans were $440,368 and $252,700, respectively.

18. Subsequent Events:

Management has evaluated subsequent events through the date these financial statements were issued. Based on our evaluation, the following disclosures have been made:

License Agreement

On January 29, 2019, the Company amended and restated the following agreements: (i) the License Agreement, dated February 4, 2015, as amended, between the Company and UCL Business, Plc ("UCLB"); (ii) the License Agreement, dated July 28, 2017, as amended, between the Company and UCLB; and (iii) the License Agreement, dated March 15, 2018, between the Company and UCLB to establish new stand-alone license agreements for the following inherited retinal disease programs: (a) achromatopsia ("ACHM") caused by mutations in CNGB3; (b) ACHM caused by mutations in CNGA3; (c) X-linked retinitis pigmentosa ("XLRP"); and (d) RPE65-mediated IRD.

The Company's obligation to pay UCLB a share of certain sublicensing revenues, as was provided under the February 4, 2015 agreement, has been removed from each of the stand-alone agreements. Each of the stand-alone agreements now reflects terms substantially similar to those of the March 15, 2018 agreement.

Additionally, the new stand-alone agreement related to CNGB3 provides for the Company to pay UCLB an upfront payment of £1,500,000, or approximately $1,976,000, and issue £1,500,000 of the Company's ordinary shares.

Collaboration Agreement

On January 30, 2019, (the "Agreement Date"), the Company entered into a Collaboration Agreement with Janssen Pharmaceuticals, Inc. ("Janssen") for the research, development and commercialization of gene therapies for the treatment of inherited retinal diseases ("IRDs").

Under the terms of the agreement, the Company will receive a $100 million cash upfront payment. 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 products globally. The Company will manufacture these products for commercial supply. Janssen will pay 100% of the clinical and commercialization costs of the products and the Company is eligible to receive untiered 20 percent royalties on net sales of products and additional development and commercialization milestones of up to $340 million. In addition, the Company and Janssen have entered into a research collaboration in the area of IRDs, 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 IND. Janssen will then pay 100% of the clinical and commercialization costs for these products and the Company will receive an untiered royalty on net sales in the high teens as well as development milestones. In addition, Janssen and the Company have entered into a manufacturing research collaboration to further develop processes for manufacturing AAV viral vectors in which the costs of the research will be shared.

Private Placement

On February 27, 2018, the Company issued 5,797,102 Ordinary Shares in a private placement for gross proceeds of $80 million, excluding offering costs of approximately $2.6 million. Johnson & Johnson Innovation – JJDC, Inc., the investment arm of Johnson and Johnson, led the offering and purchased 2,898,550 of the Ordinary shares issued on the same terms and conditions as the other investors in the offering.

In connection with the offering, the Company also entered into a registration rights agreement whereby, promptly following the date on which the Company becomes eligible to use a registration statement on Form S-3, but in no event later than July 31, 2019, the Company shall prepare and file a registration statement covering the resale of all of the Registrable Securities, as defined in the agreement. The Company shall use commercially reasonable efforts to have the registration statement declared effective as soon as practicable. If the registration statement is not declared effective prior to the 120th day after July 31, 2019 (or the 150th day if the Securities and Exchange Commission reviews such registration statement), then the Company will make pro rata payments in cash to each investor then holding Registrable Securities, as liquidated damages, in an amount equal to 1% of the aggregate amount invested by such investor for each thirty (30)-day period or pro rata for any portion thereof following the date by which such registration statement should have been effective.

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 as of December 31, 2018.

Exemption from Management's Report on Internal Control Over Financial Reporting

This Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

In addition, for so long as we qualify as an "emerging growth company" as defined under the JOBS Act, our independent registered accounting firm is not required to issue an attestation report on our internal control over financial reporting.

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 three months ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

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 2019 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2018.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item is incorporated by reference to our definitive proxy statement for our 2019 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2018.

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, 2018)

The following table provides information as of December 31, 2018, 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)	1,603,765	$5.34	—
2018 Plan (2)	1,658,600	$9.87	1,396,396
2018 ESPP (3)	—	—	509,166
Equity compensation plans not approved by shareholders	—	—	—
Total	3,262,365	$7.64	1,905,562

(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) 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 2019 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2018.

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 2019 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2018.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item is incorporated by reference to our definitive proxy statement for our 2019 annual shareholder meeting to be filed with the SEC within 120 days of the fiscal year ended December 31, 2018.

PART IV

ITEM 15. EXHIBITS

(a) List of documents filed as part of this Form 10-K:

(1) Financial Statements

The financial statements included in Part II, Item 8 of this document are filed as part of this Form 10-K.

(2) Financial Statement Schedules

All schedules have been omitted because they are not required or because the required information is given in the consolidated financial statements or notes thereto.

(3) Exhibits

The following documents are filed as exhibits to this Form 10-K.

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
2.1†	Agreement and Plan of Merger, dated October 5, 2018, by and among MeiraGTx Holdings plc, Vector Neurosciences Inc., VN Acquisition, Inc., VN Acquisition 2, Inc., the Vector stockholders named therein and the Vector stockholder representative, Stephen Kaplitt.					*
3.1	Restated Articles of Association of the Registrant.	S-1	333-224914	3.1	5/29/18	
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		333-224914	4.2	6/4/18	
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.	S-1/A	333-224914	10.3	5/29/18	
10.4#	Form of Indemnification Agreement for Directors and Officers.	S-1/A	333-224914	10.4	5/29/18	
10.5	Lease Agreement, dated June 29, 2016, as amended, between MeiraGTx Limited and ARE-East River Science Park LLC.	S-1	333-224914	10.5	5/14/18	

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
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	
10.12#	UK Sub-Plan Under the 2018 Incentive Award Plan.					*
10.13#	Form of Option Grant Notice and Option Agreement Under the UK Sub-Plan to the 2018 Incentive Award Plan.					*
10.14#	Employment Offer Letter, dated October 2, 2018, between MeiraGTx Holdings plc and Katherine Breedis	8-K	001-38520	10.1	10/9/18	
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	8/08/18	
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	8/08/18	
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	

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
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.					*
10.20†	License Agreement (RPE65), dated January 29, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx UK II Limited and MeiraGTx Limited.					*
10.21†	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.					*
10.22†	License Agreement (CNGA3), dated January 29, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx UK II Limited and MeiraGTx Limited.					*
10.23†	License Agreement (RPGR), dated February 5, 2019, as amended and restated by and among UCL Business PLC, MeiraGTx UK II Limited and MeiraGTx Limited.					*
10.24†	Amendment No. 4 to Exclusive License Agreement, dated January 29, 2019, between UCLB and MeiraGTx Limited.					*
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.					*
10.26†	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	
21	List of Subsidiaries					*
23.1	Consent of Ernst & Young LLP					*

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Form	File No.	Exhibit	Filing Date	Filed/ Furnished Herewith
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.					**
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	XBRL Instance Document.					*
101.SCH	XBRL Taxonomy Extension Schema Document.					*
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.					*
101.DEF	XBRL Taxonomy Definition Linkbase Document.					*
101.LAB	XBRL Taxonomy Label Linkbase Document.					*
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.					*

* 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

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 26, 2019

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 26, 2019
/s/ Katherine Breedis Katherine Breedis	Chief Financial Officer (Principal Financial and Accounting Officer)	March 26, 2019
/s/ Keith R. Harris, Ph.D. Keith R. Harris, Ph.D.	Chairman of the Board and Director	March 26, 2019
/s/ Stuart Naylor, Ph.D. Stuart Naylor, Ph.D.	Director	March 26, 2019
/s/ Ellen Hukkelhoven Ellen Hukkelhoven	Director	March 26, 2019
/s/ Martin Indyk Martin Indyk	Director	March 26, 2019
/s/ Arnold J. Levine, Ph.D. Arnold J. Levine, Ph.D.	Director	March 26, 2019
/s/ Joel S. Marcus Joel S. Marcus	Director	March 26, 2019
/s/ Neil Mendoza Neil Mendoza	Director	March 26, 2019
/s/ Gregory S. Moss Gregory S. Moss	Director	March 26, 2019
/s/ Thomas E. Shenk, Ph.D. Thomas E. Shenk, Ph.D.	Director	March 26, 2019

BOARD OF DIRECTORS

Keith R. Harris, Ph.D.
Chairman of the Board of Directors, MeiraGTx Holdings plc; Chairman, Keith Harris & Associates

Alexandria Forbes, Ph.D.
Chief Executive Officer and President, MeiraGTx Holdings plc

Ellen Hukkelhoven, Ph.D.
Managing Director, Perceptive Advisors

Martin Indyk
Distinguished Fellow and Director of Education, Council on Foreign Relations

Arnold J. Levine, Ph.D.
Professor Emeritus, Institute for Advanced Study, Princeton University

Joel S. Marcus
Founder and Executive Chairman, Alexandria Real Estate Equities, Inc.; Co-Founder, Alexandria Venture Investments, LLC

Neil Mendoza
Provost of Oriel College, Oxford University; Founder, Bookmark Content and Communications; Chairman, Victoria Private Investment Office

Stuart Naylor, Ph.D.
Chief Development Officer, MeriaGTx Holdings plc

Thomas E. Shenk, Ph.D.
James A. Elkins Jr. Professor of Life Sciences, Department of Molecular Biology, Princeton University

EXECUTIVE OFFICERS

Alexandria Forbes, Ph.D.
President and Chief Executive Officer

Richard Giroux
Chief Financial Officer and Chief Operating Officer

Stuart Naylor, Ph.D.
Chief Development Officer

Bruce Gottlieb
General Counsel and Secretary

HEADQUARTERS

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Phone: 646-490-2695
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STOCK TRANSFER AGENT

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144 Fernwood Avenue
Edison, NJ 08837
Phone: 201-680-3155
www.Computershare.com

INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

Ernst & Young, LLP

AVAILABLE INFORMATION

We make available free of charge under the Investor Relations section of our website, www.meiragtx.com, filings we make with the Securities and Exchange Commission and other information about the Company. Filings we make with the Securities and Exchange Commission may also be accessed free of charge on the Securities and Exchange Commission's publicly available website, www.sec.gov

INVESTOR RELATIONS

Elizabeth Broder
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