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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

☒ **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 001-36080

OPHTHOTECH CORPORATION

(Exact name of registrant as specified in its charter)

Delaware	**20-8185347**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
One Penn Plaza, 35th Floor **New York, NY**	**10119**
(Address of principal executive offices)	(Zip Code)

(212) 845-8200

(Registrant's telephone number, including area code)

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.001 par value	The Nasdaq Stock Market LLC

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 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 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, a 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 voting and non-voting common equity held by non-affiliates of the registrant was approximately $98.5 million, based on the closing price of the registrant's common stock on June 29, 2018.

The number of shares outstanding of the registrant's class of common stock, as of February 27, 2019: 41,421,548

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report incorporates by reference information from the definitive Proxy Statement for the registrant's 2019 Annual Meeting of Shareholders, which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2018.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "goals," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the potential benefits of our business plan and strategy to develop Zimura® (avacincaptad pegol) in geographic atrophy secondary to dry age-related macular degeneration and autosomal recessive Stargardt disease, to progress the development of our HtrA1 inhibitor program in geographic atrophy secondary to dry age-related macular degeneration, to develop our gene therapy product candidate for rhodopsin-mediated autosomal dominant retinitis pigmentosa, to develop gene therapy product candidates for Best vitelliform macular dystrophy and other bestrophinopathies for which we hold an exclusive option, and to potentially further expand our product pipeline, including through our collaborative gene therapy sponsored research programs;
- the advantages and limitations of inhibition of the complement system and HtrA1, gene therapy and other mechanisms of action in which we are pursuing development of our product candidates;
- our expectations related to our use of available cash;
- our estimates regarding expenses, future revenues, capital requirements and needs for, and ability to obtain, additional financing;
- the timing, costs, conduct and outcome of our ongoing research and preclinical development activities, including statements regarding the timing of the initiation of and completion of these activities, and the costs to obtain and timing of receipt of results from, and the completion of, such activities;
- the timing, costs, conduct and outcome of our ongoing clinical trials, including statements regarding the timing of the initiation of and completion of such trials, and the costs to obtain and timing of receipt of initial results from, and the completion of, such trials;
- our ability to in-license or acquire additional products, product candidates or technologies to treat ophthalmic diseases and the timing, costs, conduct and outcome of preclinical development or clinical trials we undertake for these newly acquired assets;
- the timing of and our ability to obtain marketing approval of our product candidates, and the ability of our product candidates to meet existing or future regulatory standards;
- the potential advantages of our product candidates and other technologies that we are pursuing;
- the rate and degree of potential market acceptance and clinical utility of our product candidates, if approved;
- our estimates regarding the potential market opportunity for our product candidates;
- the potential receipt of revenues from future sales of our product candidates, if approved;
- our sales, marketing and distribution capabilities and strategy;
- our ability to establish and maintain arrangements for the manufacture of our product candidates;
- our intellectual property position;

- the impact of existing and new governmental laws and regulations; and
- our competitive position.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and our stockholders should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report on Form 10-K are made as of the date of this Annual Report on Form 10-K, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

PART I

Item 1. Business

Overview

We are a science-driven biopharmaceutical company specializing in the development of novel therapies to treat ophthalmic diseases, with a focus on age-related and orphan retinal diseases. We are seeking to leverage our development platform, clinical experience and retina expertise to develop both therapeutics and gene therapies in these disease areas. We believe gene therapy as a treatment modality holds tremendous promise for ophthalmic diseases. We also believe therapeutics will continue to serve an important role in ophthalmic drug development, particularly as treatments with novel mechanisms of action are developed and brought to market and as the long-term effects of these treatments continue to be understood. Our team has significant ophthalmic drug development experience and deep relationships with global ophthalmology thought leaders. We have an extensive network of ophthalmic clinical trial sites, having worked with over 250 sites worldwide. We believe that the combination of these factors, together with our experience in designing and executing investigational new drug, or IND, -enabling studies and clinical trials for eye diseases, and specifically back of the eye diseases, provide us a competitive advantage.

We currently have ongoing research and development programs for both therapeutics and gene therapy product candidates and technologies.

Our therapeutics portfolio consists of Zimura® (avacincaptad pegol), which is a C5 complement inhibitor, and our program of High temperature requirement A serine peptidase 1 protein, or HtrA1, inhibitors. We have Phase 2b clinical trials ongoing evaluating Zimura for the treatment of:

- geographic atrophy, or GA, which is a late-stage form of dry age-related macular degeneration, or AMD, characterized by retinal cell death and degeneration of tissue in the central portion of the retina, referred to as the macula, and which may result in loss of vision; and
- autosomal recessive Stargardt disease, or STGD1, which is an orphan inherited retinal disease, or IRD, that also may result in loss of vision.

We previously also evaluated Zimura in combination with Lucentis® (ranibizumab), an anti-vascular endothelial growth factor, or anti-VEGF, agent, for the treatment of wet AMD, for which we completed a Phase 2a clinical trial during the fourth quarter of 2018. We do not currently have plans to develop Zimura further in wet AMD. Our HtrA1 inhibitor program, which we are developing for GA secondary to dry AMD and potentially other age-related retinal diseases, such as wet AMD and idiopathic polypoidal choroidal vasculopathy, or IPCV, is in the preclinical stage of development.

Our gene therapy portfolio consists of several ongoing research and preclinical development programs that use adeno-associated virus, or AAV, for gene delivery. These AAV gene therapy programs are targeting the following orphan IRDs:

- rhodopsin-mediated autosomal dominant retinitis pigmentosa, or RHO-adRP, which is characterized by progressive and severe bilateral loss of vision leading to blindness;
- Best vitelliform macular dystrophy, or Best disease, which is characterized by bilateral egg yolk-like macular lesions that, over time, progress to atrophy and loss of vision, and potentially other diseases associated with mutations in the *Best1* gene, which we refer to as bestrophinopathies;
- Leber Congenital Amaurosis type 10, or LCA10, which is characterized by severe bilateral loss of vision at or soon after birth; and
- autosomal recessive Stargardt disease.

Therapeutic Development Programs

Zimura Clinical Programs

Zimura, our C5 complement inhibitor, is a chemically-synthesized, pegylated RNA aptamer. Aptamers are short molecules made up of a single stranded nucleic acid sequence or amino acid sequence that binds molecular targets with high selectivity and specificity. We currently have two clinical trials for Zimura ongoing. These clinical trials are designed to obtain data to guide potential future development efforts and are not intended to be pivotal studies. The following is a brief description of these trials and their current status:

- **OPH2003 (geographic atrophy (GA) secondary to dry AMD)**: an ongoing, randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy in patients with GA secondary to dry AMD. We completed enrollment for this clinical trial in October 2018 with a total of 286 patients enrolled. We expect that initial, top-line data from this clinical trial will be available during the fourth quarter of 2019.
- **OPH2005 (autosomal recessive Stargardt disease (STGD1))**: an ongoing, randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy for the treatment of STGD1. We completed enrollment for this clinical trial in February 2019 with a total of 95 patients enrolled. We expect that initial, top-line data from this clinical trial will be available during the second half of 2020.

HtrA1 Inhibitor Program

We are pursuing the preclinical development of certain HtrA1 inhibitors, to which we acquired rights through our October 2018 acquisition of Inception 4, Inc., or Inception 4, for the treatment of GA secondary to dry AMD. Our HtrA1 inhibitor program includes a number of lead small molecule compounds that show high affinity and specificity for HtrA1 when tested, as well as a number of backup compounds. We are pursuing formulation development studies with the goal of identifying a formulation for intravitreal application in the eye. If we are successful in identifying and formulating a product candidate from this program, we plan to initiate IND-enabling activities for the selected product candidate. Based on current timelines and subject to successful completion of preclinical development, we are currently targeting submission of an IND to the U.S. Food and Drug Administration, or FDA, for a product candidate from this program for the treatment of GA secondary to dry AMD by late 2020.

Gene Therapy Research and Development Programs

RHO-adRP Product Candidate

We are pursuing the preclinical development of our novel AAV gene therapy product candidate for the treatment of RHO-adRP, to which we acquired exclusive development and commercialization rights through a June 2018 license agreement with the University of Florida Research Foundation, or UFRF, and the University of Pennsylvania, or Penn. We and Penn are conducting additional preclinical studies of the RHO-adRP product candidate and a natural history study of RHO-adRP patients. In parallel, we have commenced IND-enabling activities for the RHO-adRP product candidate, including manufacturing for preclinical toxicology studies. We have engaged a gene therapy contract development and manufacturing

organization, or CDMO, as the manufacturer for preclinical and Phase 1/2 clinical supply of our RHO-adRP product candidate. Based on current timelines and subject to regulatory review, we expect to initiate a Phase 1/2 clinical trial for this product candidate during 2020.

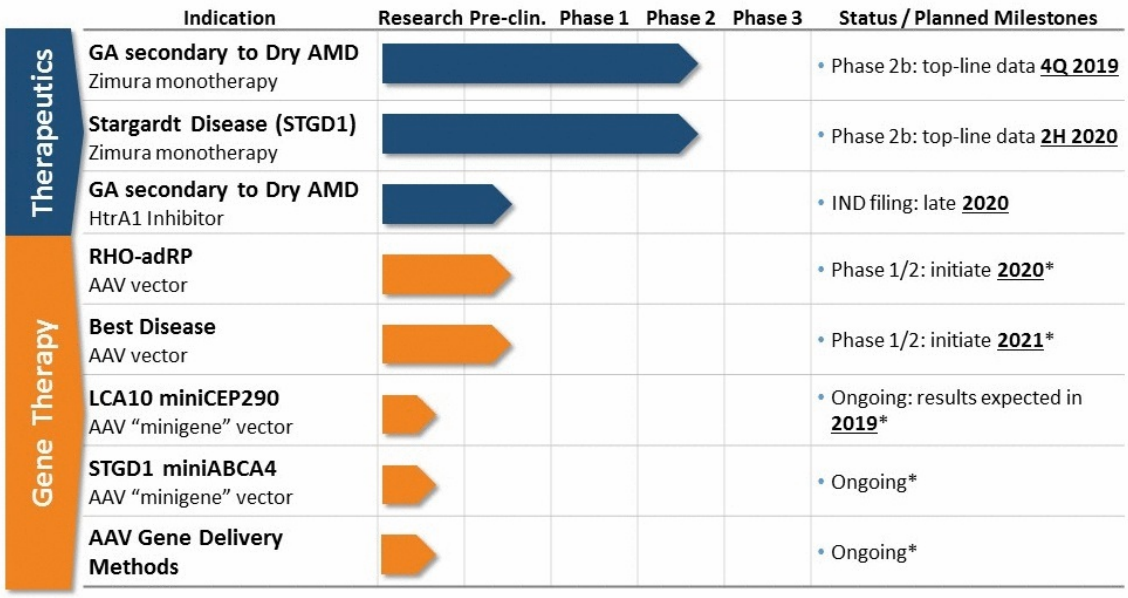
Bestrophinopathies Program

We have an exclusive option agreement with Penn and UFRF to acquire an exclusive, global license to develop and commercialize novel AAV gene therapy product candidates for the treatment of Best disease and other bestrophinopathies. We and Penn are conducting additional preclinical studies of a product candidate from this program and natural history studies of patients with bestrophinopathies. In parallel, we are planning to commence IND-enabling activities for a product candidate from this program, including manufacturing for preclinical toxicology studies. We have recently engaged a CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of this product candidate. Based on current timelines and subject to regulatory review and execution of a definitive license agreement with Penn and UFRF, we expect to initiate a Phase 1/2 clinical trial for a product candidate from this program during 2021.

University of Massachusetts Medical School Research (LCA10 and STGD1; Gene Delivery Methods)

We are funding three sponsored research programs at the University of Massachusetts Medical School, or UMMS. Two of these programs consist of utilizing a "minigene" approach to create AAV gene therapy product candidates targeting LCA10 and STGD1. AAV vectors are generally limited as a delivery vehicle by the size of their genetic cargo, which is restricted to approximately 4,700 base pairs of genetic code. The use of "minigenes" seeks to deliver a smaller but still functional form of a larger gene packaged into a standard-size AAV delivery vector. The third program consists of evaluating various AAV gene delivery methods for potential application in the eye. UMMS has granted us an option to obtain an exclusive license to any patents or patent applications that result from any of these sponsored research programs. The sponsored research at UMMS is ongoing and we expect to receive results from the sponsored research for LCA10 during 2019, at which point we may elect to exercise our option to in-license the LCA10 program.

The following table summarizes the current status of our ongoing research and development programs:



* We have an option to exclusively in-license intellectual property resulting from ongoing sponsored research.

Business Development Activities

In 2018, we continued to implement a business development strategy, which we started to undertake in early 2017, based on reviewing our strategic alternatives in light of our deep expertise and experience in ophthalmic drug development and

our business plan. Without limiting any option, the principal focus of this strategy was to actively explore obtaining rights to additional products, product candidates and technologies to treat ophthalmic diseases, particularly those in the back of the eye. These efforts have resulted in the expansion of our research and development pipeline, with the initiation of our gene therapy sponsored research programs with UMMS in February 2018, the in-license of our RHO-adRP gene therapy product candidate in June 2018, the acquisition of our HtrA1 inhibitor program in October 2018 and the entry into our exclusive option agreement with Penn and UFRF for gene therapy product candidates for bestrophinopathies in October 2018. We expect to continue to evaluate opportunities to potentially obtain rights to additional gene therapy and therapeutic product candidates on a selective basis. We intend to continue to focus on opportunities that present a compelling scientific rationale, have the potential to address an unmet medical need and present a meaningful commercial opportunity. To the extent feasible, we plan to target opportunities where we believe third-party funding for specific programs or technologies may be available.

Eye Diseases

Eye diseases can be caused by many factors and can affect both the front or back of the eye. In more severe cases, eye diseases can result in total loss of vision. In the developed world, the most common eye diseases that can result in total loss of vision are those affecting the retina and optic nerve, including AMD, diabetic retinopathy and glaucoma. These diseases deprive patients of their sight and, as a result, impair their ability to live independently and perform daily activities. Any improvement in vision, or even a slowing of the rate of progression of vision loss, has a tremendous impact on the quality of life of people with impaired vision. There are many other eye diseases that are less common but still represent an unmet medical need, particularly orphan IRDs that are associated with mutations in a single gene, referred to as monogenic, that lead to retinal degeneration and vision loss, generally in younger patients. We believe that these disease areas present several potential opportunities for ophthalmic drug development. A 2014 report from Prevent Blindness, a patient advocacy group, estimated that the total real annual costs in the United States related to eye diseases and vision problems expressed in constant 2014 dollars would increase from $145 billion in 2014 to $376 billion by 2050.

Age Related Macular Degeneration

AMD is a disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina responsible for sharp vision. AMD is characteristically a disease of the elderly and is the leading cause of blindness in individuals over the age of 50 in developed countries. There are two forms of AMD, dry AMD and wet AMD. Most AMD patients initially present with dry AMD, which generally progresses slowly over multiple years and may ultimately result in GA, which is characterized by degeneration of tissue in the macula. By contrast, wet or neovascular AMD, which is characterized by the growth of abnormal new blood vessels under and into the retina, although less prevalent, is more likely to cause sudden, often substantial, loss of vision.

According to Brightfocus Foundation, approximately 11 million people in the United States have some form of AMD, including both early and late stages of the dry and wet forms. We estimate that there are a similar number of affected individuals in France, Germany, Italy, Spain and the United Kingdom, which are the five major market countries for pharmaceutical treatments in Western Europe, commonly referred to as the EU5, as these countries, in the aggregate, have a population similar to that of the United States. As the populations in the United States and Western Europe continue to age, we expect that these numbers will increase. In addition to having a devastating effect on patients, AMD also has a significant impact on the economy. According to a 2010 study sponsored by AMD Alliance International, the annual direct healthcare system costs of visual impairment worldwide due to AMD were estimated at approximately $255 billion.

Dry AMD

Dry AMD is a significant cause of moderate and severe loss of vision, affecting vision in both eyes in most patients. Although dry AMD is the most common form of AMD, there are no FDA or European Medicines Agency, or EMA, approved therapies to treat this condition. In dry AMD, thinning of the retinal pigment epithelial, or RPE, cells in the macula develops, along with other age-related changes to the adjacent retinal and choroidal tissue layers. The RPE is a layer of cells within the retina on which photoreceptors, the cells in the retina that are responsible for capturing light and converting it to electrochemical signals to the brain, are dependent for nutrients, waste disposal and other needs. Dry AMD is typically associated with yellow-white dots or deposits under the RPE, known as drusen. Unlike in wet AMD, there is no abnormal new blood vessel growth, or neovascularization, in dry AMD. The presence of drusen, in the absence of pathological neovascularization, is critical for making the diagnosis of dry AMD in patients over 50 years of age.

The progression of visual outcomes for patients with dry AMD is variable. Most patients experience mild to moderate loss of visual function, manifesting in blurring of central vision in the affected eye, as a result of progressive degeneration of

the light-sensitive photoreceptor cells in the macula. There are two instances in which visual loss from dry AMD may lead to severe vision loss:

- *Geographic Atrophy*. The progression of dry AMD with age can result in a severe form of retinal degeneration called GA, which typically leads to profound and irreversible vision loss. GA is readily diagnosed during retinal examination using standard diagnostic instruments utilized by ophthalmologists. GA appears as abrupt and deep levels of macular tissue loss, with sharp margins of characteristic degeneration compared to surrounding healthier macular tissue, which results in progressive and chronic degeneration of the retina characterized by variable thinning and dysfunction of retinal tissue. A comprehensive epidemiology study published in 2004 in *Archives of Ophthalmology* estimated that there were approximately 1 million people in the United States with GA.

- *Conversion to Wet AMD*. Dry AMD progresses to the wet form of the disease in approximately 10% – 15% of patients, leading to more rapid and further visual loss. Wet AMD occurs when new and abnormal blood vessels proliferate under or within the retina. These abnormal new blood vessels originate beneath the retina, in a layer called the choroid, and invade into the overlying retinal layers. Unlike dry AMD, there are FDA-approved therapies for wet AMD, of which the current standard of care is the administration of anti-VEGF monotherapy agents by intravitreal injection.

The absence of treatment options for dry AMD represents an area of urgent unmet medical need, and a major public health concern for the rapidly increasing elderly population. As progressive atrophy is associated with vision loss, a treatment that results in the slowing of the progression of atrophy would represent a significant medical advancement.

Inherited Retinal Diseases

Inherited retinal diseases, or IRDs, are a group of eye disorders caused by one or more inherited gene mutations that result in lack of functional proteins necessary for normal vision. Generally, IRDs are severe and progressive and will result in vision loss or blindness, either at birth or in early childhood, or gradually over time. IRDs are generally orphan diseases, meaning that these diseases affect fewer than 200,000 individuals in the United States. Partially due to their orphan nature, there are no approved treatment options available for most IRDs. Recently, gene therapies have emerged as potential therapies for monogenic IRDs, where a mutation to a single gene has been identified as the cause.

Humans generally inherit a complete set of genes from each of their parents, and therefore have two copies, or alleles, for each gene, either of which may carry a mutation, and either, or both, of which may be expressed in particular cells throughout the body. An inherited condition is referred to as autosomal recessive when the subject must inherit mutated alleles from each parent for the condition to manifest. An inherited condition is referred to as autosomal dominant when the subject must only inherit one mutated allele from either parent for the condition to manifest. The predominant or standard, non-mutated form of a gene is referred to as the wildtype form, and the protein resulting from expression of the wildtype gene is referred to as wildtype protein. In autosomal recessive conditions, because both alleles for a particular gene carry a mutation, the subject cannot produce any wildtype protein, and instead the proteins that are expressed, if any, have either limited or no function. In autosomal dominant conditions, a number of factors may contribute to the condition:

- a subject may express only the mutant allele and not the wildtype allele, resulting in production of only protein with limited or no function and not the wildtype protein;
- a subject may be expressing both alleles, but because of the mutation on one of the alleles, the amount of functional protein may not be sufficient; or
- the protein expressed by the mutant allele may be toxic to the cells in which it is produced.

Stargardt Disease

Stargardt disease is an IRD that causes progressive damage to the macula and retina, leading to loss of vision in children and adolescents. Multiple sources, including the National Eye Institute and Genetics Home Reference, both of which are affiliated with the U.S. National Institutes of Health, or NIH, estimate the prevalence of Stargardt disease to be between 1 in 8,000 and 1 in 10,000, implying that in the United States and EU5 on a combined basis, there are a total of 62,000 to 77,000 affected persons. The most common form of Stargardt disease is the autosomal recessive form, which we refer to as STGD1. STGD1 is caused by mutations in the *ATP-binding cassette, subfamily A, number 4*, or *ABCA4* gene, which is responsible for making a protein that helps to clear byproducts resulting from the visual cycle from inside photoreceptor cells in the eye.

There are currently no therapies approved by the FDA or EMA to treat Stargardt disease. The FDA has recognized Stargardt disease as an orphan disease, with several treatments in development having received orphan drug designation from the FDA.

Rhodopsin-Mediated Autosomal Dominant Retinitis Pigmentosa

RHO-adRP is a form of retinitis pigmentosa, or RP. RP is the most prevalent IRD and is typically characterized by the initial degeneration of the rod photoreceptors, which are responsible for low light vision and peripheral vision. The degeneration of the rod photoreceptors over time leads to the degeneration of the cone photoreceptors, which are the photoreceptors in the central part of the retina that are responsible for color and sharp vision. This degeneration causes night blindness and severe and progressive visual impairment. Although often diagnosed during adolescence or young adulthood, most RP patients become legally blind by age 40.

Rhodopsin is a biological pigment found in the rod photoreceptors that is extremely sensitive to light and thus is crucial for low light vision. There are more than 150 identified mutations in the gene for rhodopsin. The presence of a mutated rhodopsin gene is linked to the occurrence of RP.

Based on disease prevalence rates contained in a study published in the *Archives of Ophthalmology* in 2007, we estimate that in the United States and EU5 on a combined basis, there are a total of approximately 11,000 affected persons with RHO-adRP. There is currently no FDA or EMA approved therapy to treat this orphan IRD.

Bestrophinopathies

Bestrophinopathies are a group of IRDs associated with mutations in the *Best1* gene. The *Best1* gene encodes a multifunctional protein known as bestrophin-1, or BEST1, which regulates chemical transport and signaling in RPE cells and helps maintain homeostasis in the subretinal space, the space between the photoreceptors and the RPE. The most common bestrophinopathy is Best vitelliform macular dystrophy, also known as Best disease, which is generally autosomal dominant and generally affects individuals in both eyes. In Best disease, the lack of functional BEST1 protein results in the formation of egg yolk-like lesions in the macula that, over time, progress to macular atrophy and permanent loss of vision. In addition, because there are over 200 known mutations in the *Best1* gene, there are other bestrophinopathies being studied, including autosomal recessive forms.

Based on disease prevalence rates contained in a study published in the *American Journal of Ophthalmology* in 2012, we estimate that in the United States and EU5 on a combined basis, there are a total of approximately 10,000 affected persons with Best disease, the substantial majority of whom we believe have the autosomal dominant form of the disease. There are currently no FDA or EMA approved therapies to treat bestrophinopathies.

Leber Congenital Amaurosis Type 10

Leber Congenital Amaurosis, or LCA, is an IRD that manifests at birth or early in childhood. It is characterized by early onset of vision loss in children leading to blindness. Affected individuals often manifest symptoms such as roving eye movements, deep-set eyes and sensitivity to bright light. There are multiple types of LCA, which are associated with mutations in different genes. The most common type is LCA10, which is caused by mutations in the *CEP290* gene. Mutations in the *CEP290* gene are believed to lead to the abnormal function and potentially loss of photoreceptor cells.

Based on disease prevalence rates contained in a study published in the *American Journal of Human Genetics* in 2006, we estimate that in the United States and EU5 on a combined basis, there are a total of approximately 2,700 to 4,100 affected persons with LCA10. There is currently no FDA or EMA approved therapy to treat LCA10.

Zimura

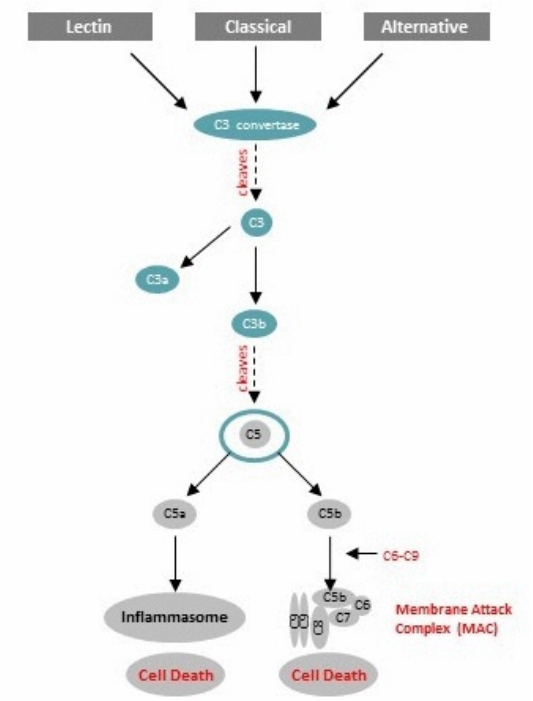
We are developing our product candidate Zimura, a C5 complement inhibitor, for the treatment of two ophthalmic conditions: GA secondary to dry AMD and STGD1. Zimura is a chemically-synthesized, pegylated RNA aptamer. Aptamers are short molecules made up of a single stranded nucleic acid sequence or an amino acid sequence. The specific three-dimensional structure of an aptamer, which results from its specific sequence, allows it to bind molecular targets with high selectivity and specificity. Zimura is a pegylated aptamer, which means that polyethylene glycol, or PEG, a common biochemical compound attached to drugs to increase their duration of action in the human body and to decrease immune response, is linked to the chemically-synthesized strand of RNA.

The Complement System and Its Potential Role in GA and STGD1

The complement system consists of a series of proteins that are involved in the defense of the host body against infectious agents, or pathogens, and other foreign proteins. The complement system modulates a variety of immune and inflammatory responses to these pathogens and foreign proteins. Under normal circumstances, complement proteins, together with antibodies and white blood cells, act beneficially to protect the host body by removing the pathogens and foreign proteins, together with other cellular debris. The complement system is generally tightly regulated, achieving the proper balance of activation and inhibition depending on the host body's requirements. Poorly regulated or aberrant activation of the complement system, without a balanced or proportional inhibition of complement proteins, may result in a variety of pathological conditions. For example, in a third-party study published in *Histology and Histopathology* in 2012, researchers found that human retinal drusen deposits, which are the hallmark of dry AMD, contained components of complement proteins.

The complement system is generally activated via one of three biological pathways commonly referred to as the classical pathway, the alternative pathway and the lectin pathway. These pathways eventually converge with the generation of an enzyme known as C3 convertase. C3 convertase cleaves, or separates, a serum protein called C3, into C3a and C3b. C3b is an important element of the body's immune response, as it binds to pathogens and makes them susceptible to destruction by white blood cells. C3b also cleaves complement protein C5. The cleavage of C5 results in the formation of the terminal complement fragments C5a and C5b. A study published in the *Journal of Biological Chemistry* in 2015 concluded that C5a primes RPE cells for inflammasome activation in the presence of waste products from the visual cycle. Inflammasomes are intracellular protein structures that lead to cell death. Formation of C5b, in combination with serum proteins C6, C7, C8 and C9, leads to the generation of C5b-9, referred to as membrane attack complex, or MAC, which has been shown to cause cell death.

A simplified illustration of the complement system and the relationships between the complement proteins appears below:



Although the causes of AMD are not completely understood—in addition to advanced age, there are environmental and genetic risk factors that contribute to the development of AMD including ocular pigmentation, dietary factors, a positive family history for AMD, high blood pressure and smoking—a body of recent scientific literature suggests that complement system activation may also contribute to the pathogenesis of AMD. A study published in the *Journal of Immunology* in 2015 concluded that MAC accumulation in RPE cells leads to mitochondrial damage and cellular dysfunction, which we believe

eventually leads to RPE cell death. Additionally, a study published in the *American Journal of Ophthalmology* in 2002 described the presence of MAC in post-mortem human donor eyes with dry AMD and GA. We believe these findings suggest that inhibition of the complement system, especially an inhibitor that prevents the cleavage of C5 into C5a and C5b, could prevent RPE cell death and potentially other pathological causes of AMD.

The pathogenesis of STGD1, which is caused by a mutation in the *ABCA4* gene, also may involve activation of the complement system. With a defective copy of the ABCA4 protein, waste byproducts that a normal ABCA4 protein would otherwise help to clear accumulate in the RPE. Waste byproducts that accumulate in the RPE are referred to as bisretinoids. We believe that the accumulation of bisretinoids in RPE cells leads to activation of the complement system and the accumulation of MAC. In RPE cells, MAC is normally cleared by lysosomes, which are organelles within cells responsible for waste degradation and disposal. Bisretinoid accumulation leads to lysosomal dysfunction, potentially preventing the clearance of MAC. MAC accumulation also negatively impacts energy production by mitochondria inside RPE cells. Bisretinoid and MAC accumulation may lead to RPE cell deterioration and contribute to the subsequent loss of photoreceptor cells, leading to a decrease in vision over time.

In April 2017, *Proceedings of the National Academy of Sciences*, or PNAS, published a study reporting on the effects of complement system modulation in the RPE of a mouse model of Stargardt disease. The researchers injected recombinant AAV containing the coding sequence for CRRY, a protein that inhibits complement system activation, into albino ABCA4 mutant mice, which led to a two-fold reduction in the accumulation of bisretinoids and a 30% increase in the number of photoreceptor nuclei at one year. The study findings indicate that the inhibition of complement activation in the albino ABCA4 mutant mice lead to healthier RPE cells as compared to RPE cells of untreated mice. Researchers at Duke University published a 2013 paper in *Investigative Ophthalmology & Visual Science,* in which they found in an *in vitro* experiment that RPE cell damage resulting from the combination of complement system activation and visual cycle waste was more damaging than either component individually. When complement factor C5 was blocked, there was a significant improvement in RPE cell viability *in vitro*. Based on the data from these *in vitro* and *in vivo* experiments, we believe molecules involved in the inhibition or regulation of the complement system and MAC activation are prime targets for therapeutic intervention in STGD1.

Zimura is designed to target and inhibit the cleavage of complement protein C5 and the formation of the terminal fragments, C5a and C5b. By inhibiting the formation of complement system terminal fragments, Zimura may decrease the activation of inflammasomes and decrease the formation of MAC, thereby potentially avoiding or slowing the degeneration of RPE cells and providing the rationale as a potential therapy for both GA and STGD1.

Our Zimura Clinical Programs

We have completed four clinical trials of Zimura to date:

- OPH2001: a Phase 1/2a clinical trial of Zimura monotherapy for the treatment of GA;
- OPH2000: a Phase 1/2a clinical trial of Zimura administered in combination with Lucentis for the treatment of wet AMD;
- OPH2007: a Phase 2a clinical trial of Zimura administered in combination with Lucentis for the treatment of wet AMD; and
- OPH2002: a very small Phase 2a clinical trial of Zimura in combination with anti-VEGF agents for the treatment of IPCV, in patients for whom anti-VEGF monotherapy had failed.

Over 160 patients have been treated with Zimura in these four completed trials, with treatment durations extending up to 48 weeks. All doses of Zimura administered in these trials were well-tolerated, with only a single adverse event, mild subcapsular cataract, assessed to be drug-related by participating investigators.

Based on our clinical experience with Zimura, the scientific literature around complement in the eye and the positive Phase 2 data for a competitor's C3 complement inhibitor in GA, we believe Zimura holds promise as a potential treatment for several ophthalmic diseases, including, GA secondary to dry AMD and STGD1. Although we previously studied Zimura for wet AMD and IPCV, we do not currently have plans to develop Zimura further in those indications. We currently have two Phase 2b clinical trials for Zimura ongoing. These clinical trials are designed to obtain data to guide potential future development efforts and are not intended to be pivotal studies. The following is a brief description of these trials and their current status:

- **OPH2003 (geographic atrophy (GA) secondary to dry AMD)**: an ongoing, randomized, double–masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy in patients with GA secondary to dry AMD. We completed enrollment for this clinical trial in October 2018 with a total of 286 patients enrolled. We expect that initial, top-line data from this clinical trial will be available during the fourth quarter of 2019.

- **OPH2005 (autosomal recessive Stargardt disease (STGD1))**: an ongoing, randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy for the treatment of STGD1. We completed enrollment for this clinical trial in February 2019 with a total of 95 patients enrolled. We expect that initial, top-line data from this clinical trial will be available during the second half of 2020.

Zimura is administered by intravitreal injection. Patients receiving intravitreal injections typically receive topical numbing drops or injection of a numbing agent prior to the injection. The administering physician also typically rinses the ocular surface with an antiseptic solution. By injecting the active agent into the vitreous cavity, the physician delivers the agent in close vicinity to the active disease site while minimizing the risk for systemic exposure to non-ocular tissues.

An intravitreal injection results in elevation of intraocular pressure, or IOP, which is usually transient. In our clinical trials, the IOP is monitored after each intravitreal injection. Certain of the dosing regimens we are evaluating in our ongoing Zimura clinical trials involve multiple intravitreal injections administered on the same day. Based on our clinical experience to date, we have not seen any meaningful or sustained increase in IOP in clinical trials involving multiple intravitreal injections on the same day, and we believe that multiple intravitreal injections likely could be delivered safely on the same day.

As we continue to develop our portfolio and evaluate our overall strategic priorities, we may out-license certain rights to Zimura if we believe the arrangement could assist us in the development or potential commercialization of Zimura and would otherwise help us pursue our business plan and strategic goals.

Our Zimura clinical experience to date, as well as our ongoing clinical trials for Zimura, are described in greater detail below.

Zimura - Dry AMD Trials

OPH2001: Completed Phase 1/2a Clinical Trial of Zimura for GA Secondary to Dry AMD

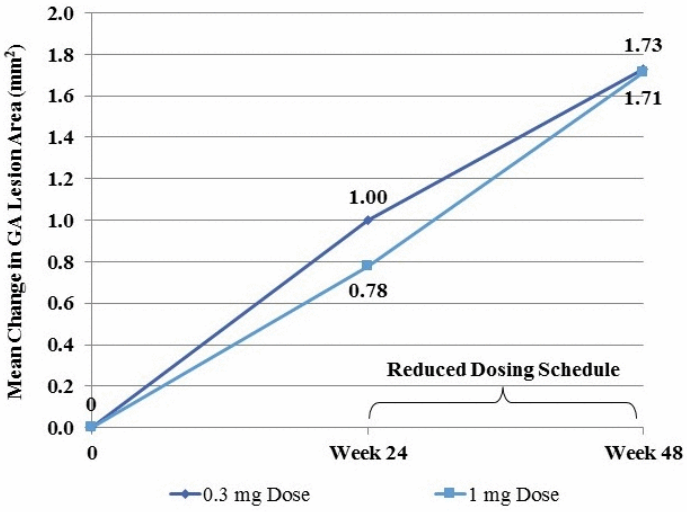
In 2011, we completed a multicenter, uncontrolled, open label Phase 1/2a clinical trial to evaluate the safety and tolerability of Zimura administered as a monotherapy in patients with GA. We enrolled 47 patients in this trial. We randomly assigned patients in this trial to one of two dose groups. Patients received a total of five intravitreal injections of either 0.3 mg or 1 mg of Zimura over a 36-week treatment period. Patients received an intravitreal injection of Zimura at day 0, week 4, week 8, week 24 and week 36 of the trial, with a final follow-up visit at week 48.

Zimura was generally well-tolerated in this trial. We did not observe any evidence of drug related adverse events. We also did not observe any incidence of conversion to wet AMD in eyes treated with Zimura. Adverse events were primarily ocular adverse events in the study eye which were related to the injection procedure.

In addition, we performed assessments of visual acuity to detect any potential decrease in vision associated with intravitreal injections, the administered drug or natural progression of the disease if left untreated. We did not identify any drug related safety issues through measurements of visual acuity.

Our Phase 1/2a clinical trial was an uncontrolled study with a small sample size and was not powered to detect a difference between Zimura dose groups, or the efficacy of Zimura monotherapy, with statistical significance. The primary purpose of the study was to assess safety and tolerability. However, during the more frequent dosing period, which is the first 24 weeks, we observed a trend, in favor of the higher of two dose groups, of a relative reduction in the mean growth of the GA lesion area, as measured by fundus autofluorescence images read by an independent reading center. Fundus autofluorescence is a common technique for photographing and documenting the size of GA present in the back of the eye, or fundus. Autofluorescence refers to the natural emission of light by biological structures. In fundus autofluorescence images, areas of atrophy are characterized by lower fluorescence.

The mean growth from baseline in the GA lesion area during the first 24 weeks of the trial, when the injections were administered more regularly, was 1.00 mm^2 for the 24 patients receiving the 0.3 mg dose and 0.78 mm^2 for the 23 patients receiving the 1 mg dose. When the injections were administered on a reduced dosing schedule during the subsequent 24 weeks, this relative trend in reduced growth in GA lesion area was no longer present. The following graph sets forth the mean change in GA lesion area from baseline for the two treatment groups over the course of the trial.



We believe this apparent trend in the relative reduction of mean growth in GA lesion area when Zimura was dosed more frequently, together with the relative loss of the benefit when Zimura was dosed less frequently, may suggest a possible drug effect.

OPH2003: Ongoing Phase 2b Clinical Trial of Zimura for GA Secondary to Dry AMD

We are currently conducting a randomized, double–masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy in patients with GA secondary to dry AMD. We initiated this trial during the fourth quarter of 2015 and initially planned to enroll 300 patients in an initial stage of the trial, with an interim analysis scheduled for the 18-month time point, and to potentially enroll up to an additional 600 patients thereafter. During 2017, based on the announcement of positive data from a competitor studying a different complement inhibitor in a Phase 2 trial in GA, we modified this trial to accelerate the timeline to obtain top-line data by reducing the number of patients in the trial to approximately 200 and shortening the time point for measuring the primary efficacy endpoint to 12 months. Prior to this initial modification taking effect, we had enrolled approximately 77 patients who were randomized into one of three treatment groups in a 1:1:1 ratio in Part 1 of the trial as follows:

- monthly intravitreal injection of 1 mg of Zimura;
- monthly intravitreal injection of 2 mg of Zimura; and
- monthly sham injection.

These patients remained in the trial following the initial modification. Following review of additional third-party clinical trial data and further statistical analysis, we decided to expand this trial to include additional patients. The approximately 209 additional patients enrolled in Part 2 of the trial were randomized into one of three treatment groups in a 1:2:2 ratio as follows:

- monthly intravitreal injection of 2 mg of Zimura plus a sham injection;
- monthly intravitreal injections of 4 mg of Zimura, administered as two injections of 2 mg of Zimura on the same day; and
- monthly sham injections, administered as two separate sham injections.

The primary efficacy endpoint is an anatomic endpoint, the mean change in rate of GA growth at 12 months, as measured by fundus autofluorescence. We plan to analyze the primary efficacy endpoint for the 2 mg treatment groups as compared to sham and for the 4 mg treatment group as compared to sham. The statistical analysis of a clinical trial outcome is primarily determined based on three factors: variability in the measured endpoint among the patient population, the magnitude of the drug effect observed in relation to that variability and the number of patients from whom data is collected in the clinical trial. Given that we have limited data regarding the effect of Zimura in GA, we determined the size of the OPH2003 trial based on our best estimates of the size of trial required to demonstrate a potential clinical benefit for Zimura. This estimate incorporates our assumptions regarding the potential performance of Zimura in this indication based in part on available third-party clinical trial data and our statistical analysis of this data, as well as our assumptions regarding the number of patients that will continue to participate in the trial through the 12-month timepoint. Given the information above, this trial could be underpowered to demonstrate a potential clinical benefit for Zimura in this indication.

We completed enrollment for this trial in October 2018 with a total of 286 patients enrolled and expect initial top-line data from this trial to be available during the fourth quarter of 2019 following the 12-month timepoint for all patients. We plan to treat and follow patients for 18 months. Treating and following patients for six months beyond the 12-month timepoint used for the primary efficacy endpoint will provide additional safety and efficacy information regarding Zimura in this indication.

Zimura - STGD1 Trials

OPH2005: Ongoing Phase 2b Clinical Trial of Zimura for STGD1

We are currently conducting a randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy for the treatment of STGD1. We completed patient enrollment for this clinical trial in February 2019 with a total of 95 patients enrolled. The patients were randomized in a 1:1 ratio as follows:

- 2 mg of Zimura, followed by 2mg of Zimura 14 days later, monthly for three months during an induction phase; followed by 4 mg of Zimura, administered as two injections of 2 mg of Zimura on the same day, monthly for 15 additional months during a maintenance phase; and

- a sham injection, followed by a sham injection 14 days later, monthly for three months; followed by two sham injections on the same day, monthly for 15 months.

We plan to evaluate the primary efficacy endpoint in this trial at 18 months. The primary efficacy endpoint is an anatomic endpoint, the mean rate of change in the area of ellipsoid zone defect, as measured by en-face spectral domain optical coherence tomography, or SD-OCT. SD-OCT is an ultra-high resolution imaging technology commonly used to visualize the retinal tissue. SD-OCT is capable of rendering images in multiple dimensions and from multiple perspectives. This imaging technology allows the demonstration of various layers of the retinal tissue, including the ellipsoid zone, which is a part of the photoreceptor cells. Scientific literature correlates defects in the ellipsoid zone with the loss of visual acuity and visual dysfunction. The ellipsoid zone is rendered in SD-OCT images as a defined layer of photoreceptor cell segments. Areas of defects in the ellipsoid zone can be detected and measured by en-face SD-OCT, which shows an SD-OCT image from the perspective of looking at the retina head-on.

We previously engaged the Foundation Fighting Blindness to provide us with data from the Foundation's publicly available ProgStar study, the largest natural history study on Stargardt disease to date. We have used this natural history data, as well as the perspectives of the key opinion leaders involved in the ProgStar study, as resources to assist in the design of the OPH2005 trial. Furthermore, our work on this clinical trial has resulted in the expansion of our network of thought leaders and clinical trial sites to include leading research university hospitals around the world, where patients with orphan retinal diseases are often referred.

We have not previously studied Zimura in STGD1 patients and thus do not have any clinical data regarding the effect of Zimura in STGD1. We had planned to enroll approximately 120 patients for this trial, which was the number of patients we believed could potentially be enrolled within a reasonable period of time. We decided, however, to cease patient enrollment during the first quarter of 2019 in light of the 18-month endpoint and our goal of providing initial top-line data from this trial by the end of 2020. We completed patient enrollment in February 2019 with a total of 95 patients enrolled. As STGD1 is an orphan indication, to our knowledge there is only very limited natural history data currently available regarding the variability of the planned primary efficacy endpoint in the STGD1 patient population we enrolled in this trial. Given the information above, this trial could be underpowered to demonstrate a potential clinical benefit for Zimura in this indication.

We expect initial top-line data from this trial to be available during the second half of 2020.

Zimura - Wet AMD Trials

OPH2000: Completed Phase 1/2a Clinical Trial of Zimura for Wet AMD

In 2009, we completed a multicenter, uncontrolled, ascending dose and parallel group, open-label, first in human Phase 1/2a clinical trial to evaluate the safety and tolerability of multiple intravitreal injections of Zimura given in combination with multiple doses of 0.5 mg of Lucentis (ranibizumab) in patients with wet AMD. We enrolled 60 patients in this trial, of which 58 were treatment-naïve patients, and two were treatment-experienced patients.

Patients were treated at one of five Zimura dose levels: 0.03 mg, 0.3 mg, 1 mg, 2 mg and 3 mg. Zimura was generally well tolerated in this trial when tested in combination with Lucentis. None of the patients experienced any dose limiting toxicities at any of the dose levels tested. We observed only a single adverse event assessed by the investigators to be related to Zimura, mild subcapsular cataract in one patient in the group treated with 2 mg of Zimura. Despite this event, this patient's visual acuity improved during the study. Adverse events were primarily ocular adverse events in the study eye which were related to the injection procedure. One patient from the 0.3 mg Zimura treatment group withdrew from the trial as a result of a serious adverse event of bacteremia unrelated to study drug or injection procedure, which resulted in a subsequent fatality. Another patient from the 0.3 mg treatment group withdrew from the trial due to the investigator's decision. Systemic adverse events in this trial were not frequently reported. No systemic adverse events were assessed as drug related.

Our Phase 1/2a clinical trial was an uncontrolled study with a small sample size and was not powered to detect a difference between Zimura dose groups or the efficacy of Zimura combination therapy with statistical significance. The primary purpose of the study was to assess safety and tolerability. In addition to our safety assessment, however, we also performed assessments of visual acuity. There was a general trend towards an improvement in visual acuity seen in all treatment groups. We focused our assessment of vision outcomes on the subgroup of 43 treatment-naïve patients who had received all six Zimura injections at the same dosage. We observed a mean increase in visual acuity from baseline at all time points for these patients, based on the number of ETDRS letters the patient could read. For this subgroup, at week 24 of the trial, we noted improvements in mean visual acuity from baseline as follows: 13.6 letters for the 13 patients receiving the 0.3 mg dose, 11.7 letters for the 15 patients receiving the 1 mg dose and 15.3 letters for the 15 patients receiving the 2 mg dose. In this subgroup, 22 patients (51%) gained at least 15 ETDRS letters, defined as significant visual gain, consisting of six patients (46%) in the 0.3 mg dose group, seven patients (47%) in the 1 mg dose group and nine patients (60%) in the 2 mg dose group.

OPH2004: Discontinued Phase 2a Trial of Zimura for Treatment-Experienced Wet AMD Patients

During the fourth quarter of 2015, we initiated an open-label Phase 2a clinical trial to evaluate Zimura's potential role when administered in combination with anti-VEGF therapy for the treatment of wet AMD in anti-VEGF treatment-experienced patients who did not respond adequately to anti-VEGF monotherapy. In 2017, following our reassessment of our Zimura development programs, we stopped enrolling patients in this trial as we determined that we would initiate a new Zimura wet AMD trial, the OPH2007 trial described below, for treatment-naïve patients. One patient continued to receive treatment in this trial until the first half of 2018. This patient did not experience any drug-related adverse events and there were no unexpected safety issues.

OPH2007: Completed Phase 2a Clinical Trial of Zimura for Treatment-Naïve Wet AMD Patients

In 2018, we completed a randomized, dose-ranging, open-label, multi-center Phase 2a clinical trial of Zimura in combination with 0.5 mg of Lucentis to evaluate the safety of different dosing regimens of Zimura in combination with an anti-VEGF agent in treating wet AMD. We enrolled a total of 64 treatment-naïve patients for this trial. We assigned patients in this trial to one of four groups:

- In Groups 1 and 2, consisting of ten patients in each group, patients received monthly combination therapy consisting of 0.5 mg of Lucentis followed by, in Group 1, 4 mg of Zimura two days later and in Group 2, 2 mg of Zimura on the same day as the Lucentis treatment;
- In Groups 3 and 4, consisting of 22 patients in each group, patients received dosages in two phases, consisting of:
    - first, an induction phase from day one to the second month, during which the patients received 0.5 mg of Lucentis followed by 2 mg of Zimura on the same day, followed by 2 mg of Zimura fourteen days later; and

- second, a maintenance phase from the third month to the fifth month, during which the patients received, in Group 3, 0.5 mg of Lucentis followed by 2 mg of Zimura on the same day and in Group 4, 2 mg of Zimura followed two days later with 0.5 mg of Lucentis and 2 mg of Zimura.

From a safety perspective, Zimura combination therapy with Lucentis was generally well tolerated after six months of treatment. The most frequently reported ocular adverse events were related to the injection procedure. We did not observe any adverse events attributable to Zimura combination therapy.

Our Phase 2a clinical trial was an uncontrolled trial with a small sample size designed to assess safety at different dosages and to detect a potential efficacy signal. This trial was not designed to detect a statistically significant difference between Zimura dose groups or to evaluate the efficacy of Zimura combination therapy with statistical significance.

We evaluated the mean change in best corrected visual acuity at the six-month timepoint as compared to baseline. The data are summarized as follows:

- In Group 1, the mean change in visual acuity was 9.0 ETDRS letters with a median of 7.0 letters, and 40% of the patients gained greater than or equal to three lines of vision, or 15 ETDRS letters, defined as significant visual gain;
- In Group 2, the mean change in visual acuity was 10.2 ETDRS letters with a median of 16.0 letters, and 60% of patients gained greater than or equal to 15 ETDRS letters;
- In Group 3, the mean change in visual acuity was 10.7 ETDRS letters with a median of 10.0 letters, and 40.9% of patients gained greater than or equal to 15 ETDRS letters; and
- In Group 4, the mean change in visual acuity was 9.9 ETDRS letters with a median of 11.0 letters, and 18.2% of patients gained greater than or equal to 15 ETDRS letters.

At this point, we have decided not to proceed with further development of Zimura in wet AMD and instead focus our resources on the development of Zimura in our clinical programs in GA secondary to dry AMD and STGD1.

Zimura - IPCV Trials

OPH2002: Completed Phase 2a Clinical Trial of Zimura for IPCV

In late 2014, we initiated a very small, uncontrolled, open-label, Phase 2a clinical trial to evaluate Zimura's potential role when administered in combination with anti-VEGF agents for the treatment of IPCV in treatment-experienced patients for whom anti-VEGF monotherapy failed. IPCV is an age-related disease that is similar to wet AMD and is commonly characterized by leakage under the RPE, subretinal hemorrhage and RPE detachment. We enrolled four patients in the trial. None of the patients had a greater than 15-ETDRS letter decrease in visual acuity, which is considered a significant loss in visual acuity, following treatment in this study. None of the patients experienced any drug-related adverse events and there were no unexpected safety issues from this trial.

OPH2006: Discontinued Phase 2a Trial of Zimura for IPCV

In late 2017, we initiated a randomized, dose-ranging, open-label Phase 2a clinical trial of Zimura in combination with Eylea® (aflibercept), an anti-VEGF agent, in treatment-experienced patients with IPCV. We did not enroll any patients in this clinical trial and decided to discontinue this clinical trial. We currently do not have any plans to further develop Zimura in IPCV.

HtrA1 Inhibitor Program

In October 2018, we acquired Inception 4, a private biopharmaceutical company owned by funds controlled by Versant Ventures. We acquired Inception 4 through a merger with our subsidiary, Orion Ophthalmology LLC, or Orion. Through this acquisition, we obtained worldwide development and commercialization rights to certain HtrA1 inhibitors. We are currently developing this program for the treatment of GA secondary to dry AMD and may in the future evaluate HtrA1 inhibition as a potential treatment modality for other age-related retinal diseases, such as wet AMD and IPCV.

The *HtrA1* gene encodes for an enzyme that may affect cellular structure, function and homeostasis, which is the dynamic equilibrium maintained in cells and tissue required for normal physiology. Genetic linkage studies, including a study published in *Molecular Vision* in 2017, show a correlation between the expression of HtrA1 and a certain set of genes conferring risk for AMD. A study of post-mortem eyes from subjects with AMD published in *EBioMedicine* in 2018 found overexpression of HtrA1 in RPE cells as compared to the eyes of non-AMD subjects. Additionally, the overexpression of HtrA1 was found, in an *in vitro* experiment published in the same article, to lead to alterations and disruptions in the morphology and function of RPE cells. Although the causal pathway between expression of HtrA1 and AMD is still not well understood, we believe that these findings suggest that HtrA1 overexpression may play a role in AMD and that molecules involved in the regulation and inhibition of HtrA1 may have therapeutic benefit in the treatment of dry AMD, including GA, as well as potentially other age-related retinal diseases, such as wet AMD and IPCV.

Our HtrA1 inhibitor program includes a number of lead small molecule compounds that show high affinity and specificity for HtrA1 when tested *in vitro* and target engagement when tested in multiple animal models, as well as a number of backup compounds. We are pursuing formulation development studies with the goal of identifying a formulation for intravitreal application in the eye. If we are successful in identifying and formulating a product candidate from this program, we plan to initiate IND-enabling activities for the selected product candidate.

In connection with our acquisition of Inception 4, we also received approximately $6.1 million in cash, which we believe will be sufficient to fund the substantial majority of anticipated development costs associated with this program through the IND submission stage. Based on current timelines and subject to successful completion of preclinical development, we are currently targeting submission of an IND to the FDA for a product candidate from this program for the treatment of GA secondary to dry AMD by late 2020.

Gene Therapy Research and Development Programs

As we continue to evaluate the unmet medical needs for orphan and age-related retinal diseases, as well as the available technologies in development to potentially address these needs, we have been particularly encouraged by the prospects for gene therapy as a potential treatment modality in ophthalmology.

In February 2018, we announced that an element of our strategy would include initiating collaborative gene therapy programs focused on discovering and developing novel gene therapy technologies to treat retinal diseases, including through collaborations with leading companies and academic research institutions in the United States and internationally. To date, we have established gene therapy programs with three leading academic research institutions in the United States. These programs are described in detail below.

The Potential of Gene Therapies for Ophthalmic Diseases

Gene therapy consists of delivering DNA encoding for a functional protein to a target tissue to facilitate protein synthesis using a recipient's existing cellular machinery. Gene therapy can be used to replace a non-functional protein produced innately by the subject as a result of a genetic mutation or as a means of producing and delivering a therapeutic protein that would not otherwise be produced within the body. Many IRDs are monogenic, meaning they are caused by mutations in a single gene, and therefore could potentially be addressed by a gene replacement approach. For genetic diseases where the mutant protein has toxic effect, we have been encouraged by the potential for a “knockdown” and “replace” approach in which gene therapy not only can introduce a healthy or wildtype version of the gene into the host body but also can suppress the expression of the mutant gene. Furthermore, because gene therapy may result in a lasting, or even permanent, addition to a host body's genetic code, gene therapy has potential for an extended treatment effect through a single administration. We therefore believe that gene therapy also holds promise as a potential treatment for age-related and other non-orphan retinal diseases, especially for diseases where patients might otherwise require chronic therapy over years, if not decades.

Currently, most gene therapies for application in the eye are administered via subretinal injection. Subretinal injection is a surgical procedure in which the gene therapy vector is injected by a retinal surgeon into the potential space between the photoreceptors and the RPE and often as close as practicable to the site of desired protein expression. Once the vector is present in the target tissue area, the process by which the gene of interest is inserted into host cells by the delivery vehicle can begin. This process is referred to as transduction and the gene therapy delivery vehicle is referred to as a vector.

Gene Therapy Products and AAV Vectors

A gene therapy product typically includes the gene of interest, or transgene, together with a promoter sequence. The composition of the transgene may differ from that of the wildtype form of the gene—for example, the gene may be modified to

increase the expression of the target protein. Promoters are DNA sequences that are linked to a gene and control the transcription of a gene into RNA in the host body's cells. There are cell-specific promoters, which tend to drive gene expression in particular cell or tissue types - for example, the RPE and photoreceptors. The choice of the specific promoter that is to be linked to a transgene is an important consideration in constructing a gene therapy product.

The promoter-transgene combination is packaged together into a delivery vehicle to facilitate localization within the relevant tissue within the body. Gene therapies are typically delivered via viral vectors and among those, adeno-associated virus, or AAV, has become the most common choice for gene therapy applications inside the eye. AAV is a small, non-pathogenic cold virus. To create the vector, the DNA encoding the AAV viral genes is removed, disarming the virus, and is replaced with the therapeutic gene sequence. In addition to AAV, other gene delivery vehicles include vectors derived from lentivirus and non-viral based vectors.

We have particularly focused on AAV gene therapy, as AAV vectors have generally been found to transduce RPE, photoreceptors and other retinal cells at a high rate, and their safety profile in humans is relatively well-documented as compared to other delivery vehicles, such as lentiviral vectors. Gene editing approaches, such as CRISPR, in which the host DNA is modified, altered or removed via therapeutic intervention, are also emerging as a potential treatment modality for genetic diseases. Unlike lentiviral vectors or gene editing approaches, with AAV gene therapy, the delivered genetic cargo does not incorporate into or alter the host cell's existing DNA and chromosomes, but rather remains separate in the host cell's nucleus, where it can be transcribed by the host cell's existing machinery.

There are several naturally-occurring serotypes of AAV, including AAV2, AAV5, AAV8 and AAV9, as well as countless synthetic AAV serotypes. The AAV genome consists of two genetic sequences: a "Rep" gene that encodes for certain viral life-cycle proteins, and a "Cap" gene that encodes for proteins that form the viral capsid, which is the outer wall of the AAV. Recombinant AAV vectors can be created by combining the Rep sequence for one AAV serotype with the Cap sequence for a different AAV serotype. For example, a recombinant AAV 2/5 vector contains the AAV2 Rep sequence packaged within an AAV5 capsid. Because different capsid proteins have different transduction capabilities within different cell and tissue types, the selection of the capsid serotype is an important consideration in constructing an AAV gene therapy product.

One of the primary limitations with AAV gene therapy is AAV's packaging capacity: an AAV vector can hold only up to approximately 4,700 base pairs of DNA, whereas the genes for a number of IRDs, such as the *CEP290* gene implicated in LCA10 and the *ABCA4* gene implicated in STGD1, exceed that size. A possible solution to the size limitation would be to develop a "minigene" form of transgene that would be small enough to fit within the packaging capacity of AAV, but large enough for the resulting protein to maintain its function. Another potential limitation for AAV and other viral vector gene therapies is the potential to trigger an immune response. Because many types of AAV are naturally occurring, gene therapy patients may have built up neutralizing antibodies to specific AAV serotypes prior to gene therapy administration, which may result in an inflammatory immune response and tissue damage. The safety profile of AAV, however, is well-documented, and furthermore, the relative isolation of the human eye and ocular immune system within the body may mitigate the potential immune response from the administration of AAV into the eye. Our current gene therapy programs, which are described in further detail below, use AAV vectors for delivery of the genetic cargo to cells within the retina.

RHO-adRP Product Candidate

In June 2018, we entered into an exclusive global license agreement with UFRF and Penn for rights to develop and commercialize a novel AAV gene therapy product candidate for the treatment of RHO-adRP. There are over 150 known mutations in the rhodopsin gene that can result in RHO-adRP. In individuals with RHO-adRP, the rhodopsin that is produced by the mutant gene is toxic. The construct for our RHO-adRP product candidate combines in a single AAV2/5 vector:

- a transgene for a highly-efficient, novel short hairpin RNA, or shRNA, designed to target and "knockdown" production of the subject's innate rhodopsin, regardless of the specific mutation a subject has, with a
- a transgene for a healthy rhodopsin protein that is resistant to the shRNA.

Our RHO-adRP construct was tested by investigators at Penn in a naturally occurring canine model of RHO-adRP, resulting in long term, i.e., over 8 months, anatomic and functional preservation of the photoreceptors, which was demonstrated with histology and electrophysiology. The investigators had initially tested a dual vector construct in which the shRNA and the healthy rhodopsin transgenes were delivered by different AAV vectors. The investigators found, however, that the dual vector approach caused inflammation and other complications in the retina, leading the investigators to develop this single vector construct. The results from these experiments were published by scientists at Penn and the University of Florida in *PNAS* in August 2018 in a paper titled: "Mutation-independent Rhodopsin Gene Therapy by Knockdown and Replacement with a Single AAV Vector."

In addition to the exclusive license agreement, we also entered into a master sponsored research agreement with Penn, facilitated by the Penn Center for Innovation, or PCI, in June 2018, pursuant to which we, together with Penn, are conducting additional preclinical studies of the RHO-adRP product candidate and a natural history study of RHO-adRP patients.

In parallel with the sponsored research, we have commenced IND-enabling activities for the RHO-adRP product candidate, including manufacturing for preclinical toxicology studies. We have engaged a CDMO for preclinical and Phase 1/2 clinical supply of our RHO-adRP product candidate. Based on current timelines and subject to regulatory review, we expect to initiate a Phase 1/2 clinical trial for this product candidate during 2020.

Bestrophinopathies Program

In October 2018, we entered into an exclusive option agreement, or the Best Option Agreement, with Penn and UFRF, under which Penn and UFRF granted us an option to acquire an exclusive, global license to develop and commercialize novel AAV gene therapy product candidates for the treatment of Best disease and other bestrophinopathies. Investigators at Penn and UFRF tested the lead construct in a naturally occurring autosomal recessive canine bestrophinopathy model, resulting in the reversal of subretinal lesions and micro-detachments associated with the canine bestrophinopathy. The results of this work were published in *PNAS* in February 2018 in a paper titled: "*BEST1* gene therapy corrects a diffuse retina-wide microdetachment modulated by light exposure." We believe the results from these experiments in a naturally occurring canine bestrophinopathy model with distinct phenotypic similarities to human Best disease demonstrate the potential therapeutic benefit of the BEST1 gene therapy product candidates from Penn and UFRF.

In addition to the Best Option Agreement, we also entered into a master sponsored research agreement with Penn (which is separate from the master sponsored research agreement for our RHO-adRP product candidate), facilitated by PCI, pursuant to which we, together with Penn, are conducting additional preclinical studies of a product candidate from this program as well as natural history studies of patients with bestrophinopathies.

In parallel with the sponsored research, we are planning to commence IND-enabling activities for a product candidate from this program, including manufacturing for preclinical toxicology studies. We have recently engaged a CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of this product candidate. Based on current timelines and subject to regulatory review and execution of a definitive license agreement with Penn and UFRF, we expect to initiate a Phase 1/2 clinical trial for a product candidate from this program during 2021.

University of Massachusetts Medical School Research (LCA10 and STGD1; Gene Delivery Methods)

In February 2018, we entered into two sponsored research agreements with UMMS to utilize a "minigene" approach to create AAV gene therapy product candidates targeting LCA10 and STGD1. The "minigene" approach may offer a potential solution for diseases that would otherwise be difficult to address through conventional AAV gene replacement therapy where the size of the transgene exceeds the packaging capacity of conventional AAV vectors. We also entered into a separate sponsored research agreement with UMMS to evaluate various AAV gene delivery methods for potential application in the eye. UMMS has granted us an option to obtain an exclusive license to any patents or patent applications that result from these sponsored research programs.

LCA10 is caused by mutations in the *CEP290* gene. The naturally occurring *CEP290* gene is approximately 8,000 base pairs. In a January 2018 publication in *Human Gene Therapy*, researchers at UMMS demonstrated that injection of a CEP290 minigene into a newborn mice model for LCA10 resulting in rescue of photoreceptor cells, as evidenced by both anatomical and functional measures. Currently, UMMS is evaluating other CEP290 minigene fragments and promoters for potential enhanced efficacy and we expect to receive results during 2019, at which point we may elect to exercise our option to in-license the LCA10 program.

STGD1 is caused by mutations in the *ABCA4* gene. The size of the naturally occurring *ABCA4* gene is approximately 7,000 base pairs. UMMS plans to construct and evaluate several ABCA4 minigene fragments to be tested in both *in vitro* and *in vivo* experiments.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of Zimura, our HtrA1 inhibitors, our RHO-adRP product candidate, the BEST1 product candidates for which we have an option from Penn and UFRF, or any other product candidate we may develop. Although we rely and intend to continue to rely upon third-party contract manufacturing organizations, or CMOs, to produce our products and product candidates, we have personnel

with experience to manage the third-party CMOs that we have engaged or may engage to produce our product candidates. We do not have any long-term supply arrangements other than as described below.

Manufacturing of pharmaceutical and biological products is a process that generally involves procurement of starting materials, such as raw materials, chemical or biological synthesis in controlled environments and post-production testing and analysis before the product can be released. Manufacturing processes can be complex and difficult to develop, especially for biological products such as gene therapies. Even when a manufacturing process is successfully developed, there are challenges associated with scaling up a manufacturing process to produce quantities sufficient for clinical trials or potential commercial sales and producing high-quality materials consistently using a clearly defined manufacturing process. The manufacture of pharmaceutical and biological products is subject to FDA review and oversight. Having a well-defined and validated manufacturing process is crucial to obtaining FDA approval of any product candidate we may bring forward.

Zimura Manufacturing

The process for manufacturing Zimura consists of chemical synthesis, pegylation, purification and finally freeze drying to form a powder, which is the active pharmaceutical ingredient, or API. Each of these steps involves a relatively common chemical engineering process. In a separate process that follows the freeze drying, the Zimura API is dissolved in a liquid solution that includes certain chemical buffers and then is asceptically filtered into vials from which the intravitreal injection solution is drawn. This process of rendering the API into a liquid solution and placing it into vials is referred to as fill/finish services.

We currently rely upon a single third-party manufacturer, Agilent Technologies, Inc., or Agilent, to supply us with API for Zimura and a different, single third-party manufacturer, Ajinomoto Bio-Pharma Services (formerly Althea, Inc.), or Ajinomoto, to provide fill/finish services for Zimura. We currently obtain Zimura API from Agilent on a purchase order basis. We have entered into a clinical and commercial services agreement with Ajinomoto for fill/finish services for Zimura. This agreement is summarized below. We obtain the PEG reagent used to make Zimura API from a single third-party manufacturer on a purchase order basis.

Ajinomoto Clinical and Commercial Services Agreement

In October 2016, we and Ajinomoto entered into a Clinical and Commercial Services Agreement, which we refer to as the Fill/Finish Services Agreement. Pursuant to the Fill/Finish Services Agreement, Ajinomoto agreed to provide clinical and commercial fill/finish services for Zimura as well as any future product candidates that we and Ajinomoto may mutually agree. The Fill/Finish Services Agreement has an initial term that will expire at the end of 2027, absent termination by either party in accordance with the terms of the Fill/Finish Services Agreement. The initial term of the Fill/Finish Services Agreement may be extended by mutual agreement of the parties. The amount payable by us to Ajinomoto under the Fill/Finish Services Agreement is based on the volume of finished drug product that we order, subject to periodic adjustments over the term of the Fill/Finish Services Agreement. In addition, in the event that we order a specified volume of product, Ajinomoto agreed to supply biological or pharmaceutical drug products meeting certain parameters exclusively to us.

We may cancel any purchase order under the Fill/Finish Services Agreement at any time, subject to the payment of specified cancellation fees. We may terminate the Fill/Finish Services Agreement, without cause, as of any date following the third anniversary of the effective date upon six months' prior notice to Ajinomoto. Each party also has the right to terminate the Fill/Finish Services Agreement for other customary reasons such as material breach and bankruptcy.

The Fill/Finish Services Agreement contains provisions relating to compliance by Ajinomoto with current Good Manufacturing Practices, cooperation by Ajinomoto in connection with marketing applications for our product candidates, indemnification, confidentiality, dispute resolution and other customary matters for an agreement of this kind.

Gene Therapy Manufacturing

The manufacture of AAV gene therapies requires the use of high quality reagents and substrates as starting materials, such as plasmids and cells. Plasmids are circular double-stranded DNA sequences that exist separate and apart from a cell's chromosomes and which can be engineered to encode for a specific promoter-transgene combination or a specific AAV Rep-Cap combination. Cell lines that are free of microbial contamination are selected to ensure the safety and quality of the final, produced AAV vector. The plasmids and cell lines are generally sourced from a limited number of qualified suppliers.

The process for producing AAV vectors typically consists of plasmid transfection of an appropriate cell line. In this step, specifically-designed plasmids are inserted into living cells, where the AAV Rep-Cap genes are expressed using the cell's

existing machinery. Empty virus capsids are then synthesized and packaged together with the promoter-transgene combination sequence. The subsequent purification process is comprised of steps that clear host cell impurities present in the harvested material and that aid in the removal of empty virus capsids from AAV vectors containing the promoter-transgene combination sequence. Each of these closely monitored purification steps involves a relatively common biochemical engineering process. The resulting purified suspension of AAV vectors is considered the drug substance for AAV gene therapies. In a separate process that follows formulation and purification, the AAV drug substance is fill/finished into vials from which the injection solution is drawn.

We have engaged a gene therapy CDMO for preclinical and Phase 1/2 clinical supply of our RHO-adRP drug product candidate. We have recently engaged a CDMO for preclinical and Phase 1/2 clinical supply of the BEST1 gene therapy drug product candidate for which we are planning to commence IND-enabling studies.

Sales and Marketing

We expect that our commercial strategy for any of our product candidates, including whether to retain commercial rights and market and sell the product candidate ourselves or to utilize collaboration, distribution or other marketing arrangements with third parties in some or all geographic markets, will be determined based on a variety of factors, including the size and nature of the patient population, the disease area, the particular indication for which the product candidate is approved, the territory in which the product candidate may be marketed and the commercial potential for such product candidate. We are developing Zimura and our HtrA1 inhibitor program for GA secondary to dry AMD, which is a condition affecting a relatively large number of individuals, and we are also developing Zimura for STGD1, which is a condition affecting a much more limited number of individuals. Our gene therapy programs are currently being developed for orphan IRDs with a limited number of affected individuals. If any of our product candidates are approved, the size and nature of the affected patient population will be an important factor in our commercial strategy.

In addition, our commercial strategy will vary depending on whether the disease is typically treated by general ophthalmology practitioners, specialists, such as retina specialists, or other sub-specialists. For example, in the United States, retina specialists perform most of the medical procedures involving diseases of the back of the eye. Intravitreal injection and subretinal injection are specialized procedures. In the vast majority of cases in the United States, retina specialists perform intravitreal injections and highly specialized retina surgeons perform subretinal injections. We believe that retina specialists and retina surgeons in the United States are sufficiently concentrated such that we could effectively promote an approved product candidate to these specialists with a targeted specialty sales and marketing group. For example, retina specialists who see patients with IRDs, as well as their patients, are generally concentrated in a limited number of large, academic research institutions located throughout the United States.

Competition

The development and commercialization of new drug products is highly competitive. We face competition with respect to our product candidates from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies, as well as generic and biosimilar companies, worldwide. There are a number of pharmaceutical and biotechnology companies that are currently developing product candidates for the treatment of GA, Stargardt disease, RHO-adRP and LCA10, and there is at least one biotechnology company that is currently developing a product candidate for the treatment of Best disease. 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. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. We also will face similar competition with respect to any products or product candidates that we may seek to develop or commercialize in the future. In particular, many companies are pursuing gene therapy approaches for orphan and age-related retinal diseases.

Based on publicly available information, we are aware of the following research and development programs that may be competitive with programs we are pursuing. Other competitive programs may exist of which we are not aware.

Competitive considerations for Dry AMD and GA:

- There are a number of products in preclinical research and clinical development by third parties to treat dry AMD, including several that are in development for GA secondary to dry AMD. In general, these product candidates can be categorized based on their proposed mechanisms of action. The mechanisms of action for these product candidates

include inflammation suppression, such as complement system inhibitors and corticosteroids, visual cycle modulators, antioxidants and neuroprotectants, cell and gene therapies and vascular perfusion enhancers. We are aware that Apellis Pharmaceuticals, Inc., Roche AG, Novartis AG and MorphoSys AG, Hemera Biosciences, Inc., Gyroscope Therapeutics, Achillion Pharmaceuticals, Inc., and Catalyst Biosciences, Inc. each have complement inhibitors in development for dry AMD. We believe that the most advanced of these programs is Apellis's pegylated, synthetic peptide targeting complement protein C3. Following positive Phase 2 results for its C3 complement inhibitor product candidate, Apellis announced in September 2018 that it had dosed the first patient in a Phase 3 program for this product candidate. If Apellis's Phase 3 program for its C3 complement inhibitor product candidate is successful, it is likely that Apellis may obtain marketing approval for its product candidate in advance of when we could reasonably expect marketing approval for Zimura in GA or a product candidate from our HtrA1 inhibitor program in GA, if at all. Moreover, we are aware that several other companies have announced development programs for the treatment of dry AMD or GA targeting different mechanisms of action outside of the complement system.

Competitive considerations for Stargardt disease:

- There are a number of products in preclinical research and clinical development by third parties to treat Stargardt disease. We are aware that Sanofi, Acucela Inc., Alkeus Pharmaceuticals, Inc., Vision Medicines, Inc., Lin BioScience, Inc., Nightstar Therapeutics plc, ProQR Therapeutics N.V., Spark Therapeutics and Generation Bio Co. each have research or development programs in Stargardt disease. Four of these programs, Acucela, Alkeus, Vision Medicines and Lin BioScience, are exploring the use of oral therapeutics, while Sanofi, with technology provided by Oxford BioMedica plc, Nightstar and Spark are each using a gene therapy approach and ProQR is using an RNA-based approach. Acucela's product candidate is in Phase 3 development while Alkeus's and Sanofi's product candidates are each in Phase 2 development. Spark's program is in the research phase. In addition, several academic organizations have early stage programs in Stargardt disease.

Competitive considerations for RHO-adRP:

- There are a number of products in preclinical research by third parties to treat RHO-adRP. We are aware that multiple academic institutions have early stage gene therapy development programs in RHO-adRP. In addition, Nightstar Therapeutics plc has a preclinical AAV gene therapy program in RHO-adRP and ProQR Therapeutics N.V. is developing an early stage RNA-based therapeutic for RHO-adRP.

Competitive considerations for Best disease:

- We are aware that Nightstar Therapeutics plc has a preclinical AAV gene therapy program in Best disease.

Competitive considerations for LCA10:

- We are aware that Editas Medicine has a CRISPR gene editing program for LCA10, an IND for which was submitted in late 2018, ProQR Therapeutics N.V. is developing an RNA-based therapeutic for LCA10 that is currently in clinical development, and Generation Bio Co. has a preclinical program that utilizes ceDNA technology to target LCA10. In addition, several academic institutions have preclinical programs in LCA10.

Intellectual Property

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, technology and know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. We seek to protect our proprietary position, among other methods and where patent protection is available, by filing U.S. and certain foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business, and by maintaining our issued patents. For our collaborative gene therapy sponsored research programs, we are generally relying on our university collaborators to generate research and data to support new patent applications, and to file, prosecute and maintain any patents or patent applications resulting from the sponsored research. We also rely upon trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

Our patent portfolio includes the following:

- patents and patent applications in-licensed from Archemix Corp., or Archemix:
    - composition-of-matter patents covering Zimura, which have issued in the United States, the European Union, Japan and certain other jurisdictions, and which are expected to expire in Japan in 2026 and elsewhere in 2025; and composition-of-matter patent applications covering Zimura, which are pending in certain other jurisdictions, and which, if granted, are expected to expire in 2025; and
    - patents covering the treatment of certain complement mediated disorders with Zimura, Zimura for use in a method of treating certain complement mediated disorders or a composition comprising Zimura for treating certain complement mediated disorders, which have issued in the United States, the European Union, Japan and certain other jurisdictions, and which are expected to expire in the United States and Japan in 2026 and elsewhere in 2025; and
- patents and patent applications owned by Ophthotech:
    - patent applications covering formulations, methods of use for treating Stargardt disease, and other proprietary technology relating to Zimura, which are pending in the United States, the European Union, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2034; and
- patents and patent applications owned by our Orion subsidiary:
    - three families of composition-of-matter patent applications covering the lead and backup compounds in our HtrA1 inhibitor program, which are pending in the United States, the European Union, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2037; and
- patents and patent applications in-licensed from UFRF and Penn:
    - two families of composition-of-matter and method-of-treatment patent applications relating to the proprietary RHO-adRP AAV technology of UFRF and Penn, which are pending in the United States, the European Union, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2037 or 2039.

The term of individual patents depends upon the legal term for patents in the countries in which they are granted. In most countries, including the United States, the patent term is generally 20 years from the earliest claimed filing date of a non-provisional patent application in the applicable country. In the United States, a patent's term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in examining and granting a patent, or may be shortened if a patent or patent application claims patentably indistinct subject matter as another commonly owned patent or patent application having an earlier expiration date and the patentee terminally disclaims the portion of the term beyond such earlier expiration date. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration date of a U.S. patent as partial compensation for the length of time the drug is undergoing clinical development or under regulatory review while the patent is in force. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended.

Similar provisions are available in the European Union and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each drug and other factors. The expiration dates referred to above are without regard to potential patent term extension or other market exclusivity that may be available to us. See "—Government Regulation and Product Approvals" below for a description of market exclusivity mechanisms that may be available to us.

We may rely, in some circumstances, upon trade secrets to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Licensing and Other Arrangements

We are party to a number of license, acquisition and other agreements that have granted us rights to develop our product candidates and conduct our research and development programs. These agreements generally impose license fee, milestone payment, royalty payment and diligence obligations on us. Our material in-license and acquisition agreements are described below.

In the future, we may enter into additional acquisition or license agreements, particularly if we choose to acquire or in-license additional products, product candidates or other technologies and expand our product pipeline. We expect that any future acquisition or license agreements would impose similar obligations on us. In the future, we may also enter into agreements to out-license intellectual property to our collaboration and research partners to assist in the development and, if approved, commercialization of our product candidates. For example, as we continue to develop our portfolio and evaluate our overall strategic priorities, we may out-license certain rights to Zimura if we believe the arrangement could assist us in the development or potential commercialization of Zimura and would otherwise help us pursue our business plan and strategic goals.

Zimura - Archemix C5 License Agreement

In September 2011, we entered into an amended and restated exclusive license agreement with Archemix relating to anti-C5 aptamers, which we refer to as the C5 License Agreement. The C5 License Agreement superseded a July 2007 agreement between us and Archemix. Under the C5 License Agreement, we hold exclusive worldwide licenses, subject to certain pre–existing rights, under specified patents and technology owned or controlled by Archemix to develop, make, use, sell, offer for sale, distribute for sale, import and export pharmaceutical products comprised of or derived from an anti-C5 aptamer for the prevention, treatment, cure or control of human indications, diseases, disorders or conditions of the eye, adnexa of the eye, orbit and optic nerve, other than certain expressly excluded applications.

Financial Terms

In connection with the C5 License Agreement, as amended, we paid Archemix an upfront licensing fee of $1.0 million and issued to Archemix an aggregate of 2,000,000 shares of our series A-1 preferred stock and 500,000 shares of our series B-1 preferred stock. We have also paid Archemix an aggregate of $2.0 million in fees based on our achievement of specified clinical milestone events under the C5 License Agreement.

Under the C5 License Agreement, for each anti-C5 aptamer product that we may develop under the agreement, including Zimura, we are obligated to make additional payments to Archemix of up to an aggregate of $57.5 million if we achieve specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $24.5 million of such payments relating to second and third indications and $2.5 million of such payments relating to sustained delivery applications. Under the C5 License Agreement, we are also obligated to make additional payments to Archemix of up to an aggregate of $22.5 million if we achieve specified commercial milestones based on net product sales of all anti-C5 products licensed under the agreement. We are also obligated to pay Archemix a double-digit percentage of specified non-royalty payments we may receive from any sublicensee of our rights under the C5 License Agreement. We are not obligated to pay Archemix a running royalty based on net product sales in connection with the C5 License Agreement.

Diligence Obligations

We are required to exercise commercially reasonable efforts in developing and commercializing at least one anti-C5 aptamer product and in undertaking actions required to obtain regulatory approvals necessary to market such product in the United States, the European Union, and Japan, and in such other markets where we determine that it is commercially reasonable to do so.

Term and Termination

Unless earlier terminated, the C5 License Agreement will expire upon the latest of 12 years after the first commercial sale in any country of the last licensed product, the expiration of the last-to-expire valid claim of the licensed patents that covers a licensed product, and the date on which no further payments of sublicensing income are to be received by us.

Either we or Archemix may terminate the C5 License Agreement if the other party materially breaches the agreement and the breach remains uncured for a specified period. Archemix may also terminate the C5 License Agreement, or may convert our exclusive license under the agreement to a non-exclusive license, if we challenge or assist a third party in challenging the

validity or enforceability of any of the patents licensed under the agreement. We may terminate the agreement at any time and for any or no reason effective at the end of a specified period following our written notice of termination to Archemix.

HtrA1 Inhibitor Program - Inception 4 Merger Agreement

In October 2018, we and Inception 4 entered into an agreement and plan of merger, which we refer to as the Inception 4 Merger Agreement, pursuant to which we acquired Inception 4 through a merger transaction, referred to as the Inception 4 Merger. Prior to the Inception 4 Merger, Inception 4 was a privately held biotechnology company focused on the research and development of small molecule inhibitors of HtrA1 for age-related retinal diseases in humans.

As upfront consideration for the Inception 4 Merger, the former equityholders of Inception 4 received 5,044,201 shares of our common stock, and in December 2018, they received an additional 130,526 shares of our common stock following finalization of customary post-closing adjustments. As part of the transaction, we received approximately $6.1 million in cash.

Contingent Consideration

In addition, pursuant to the Inception 4 Merger Agreement, the former equityholders of Inception 4 will be entitled to receive contingent future payments from us based on the achievement of certain clinical and regulatory milestones of up to an aggregate maximum amount of $105 million, with $45 million of such potential payments relating to GA and $60 million of such potential payments relating to wet AMD. These future milestone payments will be payable in the form of shares of our common stock, calculated based on the price of our common stock over a five-trading day period preceding the achievement of the relevant milestone, unless and until the issuance of such shares would, together with all other shares issued in connection with the Inception 4 Merger, exceed an overall maximum limit of approximately 7.2 million shares, which is equal to 19.9% of the number of issued and outstanding shares of our common stock as of the close of business on the business day prior to the closing date of the Inception 4 Merger, and will be payable in cash thereafter.

Diligence Obligation

We agreed to use commercially reasonable efforts to perform the activities described in an agreed-upon development plan outlining certain activities for developing at least one HtrA1 inhibitor for the treatment of GA. Our maximum aggregate liability for any and all breaches of our obligation under the Inception 4 Merger Agreement to use commercially reasonable efforts to develop an HtrA1 inhibitor is limited to $5 million.

Other Terms and Conditions

The Inception 4 Merger Agreement contains customary representations, warranties and covenants of Inception 4 and Ophthotech. The representations and warranties generally will survive until the first anniversary of the closing date, with certain specified representations and warranties surviving to 30 months after the closing date and other specified representations and warranties surviving to the expiration of the applicable statute of limitations. The Inception 4 Merger Agreement also contains customary indemnification provisions whereby the former equityholders of Inception 4 will indemnify us and certain affiliated parties for any losses arising out of breaches of the representations, warranties and covenants of Inception 4 under the Inception 4 Merger Agreement; pre-closing tax matters; appraisal claims of former Inception 4 stockholders; any pre-closing indebtedness or expenses not previously adjusted for at the closing; fraud with respect to representations and warranties of Inception 4; and certain other matters.

RHO-adRP Gene Therapy Product Candidate - License Agreement with UFRF and Penn

In June 2018, we entered into an exclusive global license agreement with UFRF and Penn, which we refer to as the RHO-adRP License Agreement. Under the RHO-adRP License Agreement, UFRF and Penn granted us a worldwide, exclusive license under specified patent rights and a worldwide, non-exclusive license under specified know-how, including specified preclinical data, to manufacture, develop and commercialize certain AAV gene therapy products for the treatment of rhodopsin-mediated diseases. The rights granted under the RHO-adRP License Agreement included certain patent rights covering a novel AAV gene therapy product candidate intended to treat RHO-adRP.

We may grant sublicenses of the licensed patent rights and know-how without the consent of the UFRF and Penn to certain affiliates and to biopharmaceutical companies that have a minimum market capitalization at the time such sublicense is granted and may otherwise grant sublicenses of the licensed patent rights and know-how with the consent of UFRF and Penn, not to be unreasonably withheld.

Diligence Obligations

We agreed to use commercially reasonable efforts to pursue an agreed-upon development plan with the intent to develop a licensed product for sale within at least the United States and two major European countries and, subject to obtaining

marketing approval, to commercialize a licensed product in at least the United States and two major European countries. In addition, we agreed to meet specified development and commercial milestones with respect to a licensed product by specified dates, as the same may be extended under the terms of the RHO-adRP License Agreement.

Financial Terms

In June 2018, we paid a $0.5 million upfront license issuance fee in connection with entry into the agreement, as well as accrued patent prosecution expenses of approximately $30 thousand. Under the agreement, we agreed to pay an annual license maintenance fee in the low double-digit thousands of dollars, which will be payable on an annual basis until the first commercial sale of a licensed product. In addition, we agreed to reimburse UFRF for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

We further agreed to pay UFRF, on behalf of both licensors, up to an aggregate of $23.5 million if we achieve specified clinical, marketing approval and reimbursement approval milestones with respect to a licensed product and additionally, up to an aggregate of $70.0 million if we achieve specified commercial sales milestones with respect to a licensed product.

We are also obligated to pay UFRF, on behalf of both licensors, royalties at a low single-digit percentage of net sales of licensed products. Such royalties are subject to customary reductions for lack of patent coverage and loss of regulatory exclusivity. In addition, such royalties with respect to any licensed product in any country may be offset by a specified portion of any royalty payments actually paid by us with respect to such licensed product in such country under third-party licenses for patent rights or other intellectual property rights that are necessary to manufacture, develop and commercialize the licensed product in such country. Our obligation to pay royalties under the RHO-adRP License Agreement will continue on a licensed product-by-licensed product and country-by-country basis until the latest of:

- the expiration of the last-to-expire licensed patent rights covering a licensed product in the country of sale;
- the expiration of regulatory exclusivity covering a licensed product in the country of sale; and
- ten years from the first commercial sale of the applicable licensed product in the country of sale.

Beginning on the earlier of the calendar year following the first commercial sale of a licensed product and the first business day of 2031, we are also obligated to pay certain minimum royalties, not to exceed an amount in the low hundreds of thousands of dollars on an annual basis, which minimum royalties are creditable against our royalty obligation with respect to net sales of licensed products due for the year in which the minimum royalty is paid.

If we or an affiliate sublicenses any of the licensed patent rights to a third party, we will be obligated to pay UFRF, on behalf of both licensors, a low double-digit percentage of the consideration received in exchange for such sublicense, with the applicable percentage based upon the stage of development of the sublicensed product at the time we or the applicable affiliate enters into the sublicense.

If we receive a rare pediatric disease priority review voucher from the FDA in connection with obtaining marketing approval for a licensed product and we subsequently use such priority review voucher in connection with a different product candidate, we will be obligated to pay UFRF, on behalf of both licensors, aggregate payments in the low double-digit millions of dollars based on certain marketing approval and commercial sales milestones with respect to such other product candidate. In addition, if we sell such a priority review voucher to a third party, we will be obligated to pay UFRF, on behalf of both licensors, a low double-digit percentage of any consideration received from such third party in connection with such sale.

Term and Termination

Unless earlier terminated by us, the RHO-adRP License Agreement will expire upon the expiration of our obligation to pay royalties to UFRF on net sales of licensed products. We may terminate the agreement at any time for any reason upon prior written notice to UFRF. Penn or UFRF may terminate the agreement if we materially breach the agreement and do not cure such breach within a specified cure period, if we experience a specified insolvency event, if we cease to carry on the entirety of our business related to the licensed patent rights, if we cease for more than four consecutive quarters to make any payment of earned royalties on net sales of licensed products following the commencement of commercialization thereof, unless such cessation is based on safety concerns that we are actively attempting to address, or if we or an affiliate challenges or assists a third party in challenging the validity, scope, patentability, and/or enforceability of the licensed patent rights.

Following any termination of the agreement prior to expiration of the term of the agreement, all rights to the licensed patent rights and know-how granted to us will revert to UFRF and Penn.

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other legal requirements of regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs and Biologics in the United States

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. Biologic products, including gene therapy products, are licensed for marketing under the Public Health Service Act, or PHSA. The failure to comply with requirements under the FDCA or PHSA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities, including state agencies.

A drug candidate must be approved by the FDA through a new drug application, or NDA. A biologic candidate is licensed by the FDA through approval of a biologic license application, or BLA. An applicant seeking approval to market and distribute a new product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated at that clinical site;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication for which the sponsor is seeking approval and the safety, potency and purity of a candidate biologic product for each indication for which the sponsor is seeking approval;
- preparation and submission to the FDA of an application requesting marketing approval for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the application; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

Preclinical Studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, and the purity and stability of the substance, as well as *in vitro* and animal studies to assess the potential safety and activity of the product candidate for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved application. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and re-approve the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by the sponsor based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Human Clinical Trials in Support of an Application

Clinical trials involve the administration of an investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in four sequential phases, which may overlap or be combined:

- ***Phase 1.*** The product candidate is initially introduced into a small number of healthy human subjects or, in certain indications, including those for which we are developing product candidates, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- ***Phase 2.*** The product candidate is administered to 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 and optimal dosage. Phase 2a clinical trials tend to be smaller pilot studies for the

purpose of demonstrating biological activity and clinical "proof of concept." Phase 2b studies tend to be larger studies focused on finding the optimal dosage and may be controlled.

- ***Phase 3.*** These clinical trials are commonly referred to as “pivotal” studies, which denotes a study that presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a product candidate. The product candidate is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, identify adverse effects, establish the overall risk–benefit profile of the product and to provide adequate information for the labeling of the product.

- ***Phase 4.*** Post-approval studies may be required to be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the safety results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product candidate; and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA, the sponsor or the DSMB may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called “compassionate use,” is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. FDA regulations allow access to investigational drugs under an IND by the sponsor or the treating physician for treatment purposes on a case-by-case basis in certain circumstances.

In addition, the Right to Try Act, signed into law in May 2018, 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 drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Special Regulations and Guidance Governing Gene Therapy Products

The FDA has defined a gene therapy product as one that mediates its effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and which is administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient. Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. Within CBER, the review of gene therapy and related products is consolidated in the Office of Tissues and Advanced Therapies (OTAT), and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. CBER works closely with the Local Biosafety Board, a federal advisory committee, in reviewing proposed and ongoing gene therapy protocols and engaging in a public discussion of scientific, safety, ethical, and societal issues related to those protocols. The NIH and the Recombinant DNA Advisory Committee, or RAC, a federal advisory committee, also advise the FDA on gene therapy issues and other issues related to emerging technologies. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols.

The FDA has issued various guidance documents regarding gene therapies, including draft guidance documents released in July 2018 relating to gene therapies for human retinal disorders and gene therapies for rare diseases, and on January 15, 2019, the FDA issued a statement that it would issue additional guidance to facilitate the development of gene therapy products. Although the FDA has indicated that these guidance documents are not legally binding, we believe that our compliance with them is likely necessary to gain approval for any gene therapy product candidate we may develop. The guidance documents provide additional factors that the FDA will consider at each of the above stages of development and relate to, among other things, the proper preclinical assessment of gene therapies; the chemistry, manufacturing, and control information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to

investigational gene therapies when the risk of such effects is high. Further, the FDA usually 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 10 years of annual queries, either in person or by questionnaire.

If a gene therapy trial is conducted at, or sponsored by, institutions receiving the NIH funding for recombinant DNA research, a protocol and related documentation must be submitted to, and the study registered with, the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules prior to the submission of an IND to the FDA. In addition, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH will convene the RAC to discuss protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA website and may be accessed by the public.

Further, to facilitate adverse event reporting and dissemination of additional information about gene therapy trials, the FDA and the NIH established the Genetic Modification Clinical Research Information System, or GeMCRIS. Investigators and sponsors of human gene transfer trials can utilize this web-based system to report serious adverse events and to provide annual reports. GeMCRIS also allows members of the public to access basic reports about human gene transfer trials registered with the NIH and to search for information such as trial location, the names of investigators conducting trials, and the names of gene transfer products being studied.

Finally, for a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with good tissue practices, or GTP. These standards are found in FDA regulations and guidances that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission, and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing.

Review of a Product Candidate by the FDA

If clinical trials are successful, the next step in the development process is the preparation and submission to the FDA of an application. The application is the vehicle through which applicants formally propose that the FDA approve a new drug for marketing and sale in the United States for one or more indications. The application must contain a description of the manufacturing process and quality control methods, as well as results of preclinical tests, toxicology studies, clinical trials and proposed labeling, among other things. Every new product must be the subject of an approved application before it may be commercialized in the United States. Under federal law, the submission of most applications is subject to an application user fee, which for federal fiscal year 2019 is $2,588,478 for an application requiring clinical data. The sponsor of an approved application is also subject to an annual program fee, which for fiscal year 2019 is $309,915. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

Following submission of an application, the FDA conducts a preliminary review of an application generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also 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. Under the Prescription Drug User Fee Act, or PDUFA, the FDA has agreed to specified performance goals and timelines in the review process of applications, which goals and timelines depend on the type of product candidate for which review is sought and whether the sponsor has applied for and received from the FDA special review status for the particular product candidate allowing for expedited review. Special review status is available for certain products that are intended to address an unmet medical need in the treatment of a serious or life–threatening disease or condition under one of the following FDA-designations: fast track designation, breakthrough therapy designation, priority review designation and regenerative medicine advanced therapy designation. The review process and the PDUFA goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured, stored, packaged and tested. These pre–approval inspections may cover all facilities associated with an

application submission, including component manufacturing (e.g., active pharmaceutical ingredients), finished product manufacturing, and control testing laboratories. The FDA will not approve an application 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 an application, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a New Molecular Entity.

The FDA is required to refer an application for a novel product candidate to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides 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.

Under the Pediatric Research Equity Act, or PREA, an application or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product 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. With enactment of the Food and Product Administration Safety and Innovation Act in 2012, sponsors must also submit pediatric study plans prior to the submission of the assessment data required under PREA. These plans are subject to FDA review prior to commencement of the pediatric study. Product candidates that have received orphan designation are generally exempt from the requirements of PREA. In addition, a sponsor may apply for a waiver of the PREA requirements, which the FDA has indicated it will automatically grant for certain diseases that do not affect pediatric populations, such as age-related macular degeneration.

The FDA's Decision on an Application

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the application, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the product candidate's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post–market studies or surveillance programs.

Post-Approval Requirements

Products manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, or changing the manufacturing process for the approved product, are subject to additional testing and/or FDA review and approval.

In addition, manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any

third–party manufacturers that the sponsor may decide to use. Accordingly, sponsors and manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Further, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may restrict, suspend or withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- fines, warning letters or holds on post-approval clinical trials;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label.

Generic Drugs and Exclusivity

Under the Hatch-Waxman Amendments to the FDCA, the FDA is authorized to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs, which are also known as reference listed drugs, or RLDs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the FDA. An ANDA applicant does not generally rely on its own preclinical or clinical data to demonstrate safety and effectiveness but instead can rely on preclinical and clinical testing previously conducted by the sponsor of the RLD. The ANDA applicant must show that the generic version is identical to the RLD with respect to a number of factors, including the active ingredient, and that the generic version is "bioequivalent" to the RLD. Physicians, pharmacists and third-party payors generally consider an approved generic drug to be fully substitutable for the RLD.

Sponsors of RLDs are required to list in the FDA's Orange Bank each patent with claims covering the RLD or approved methods of using the RLD. An ANDA applicant is required to certify to the FDA concerning any such patents, which may be a certification that the listed patent is invalid, unenforceable or will not be infringed by the new product, which is known as a Paragraph IV certification. An ANDA applicant that makes a Paragraph IV certification must notify the sponsor of the RLD, who may then initiate a patent infringement lawsuit in response to the notice of Paragraph IV certification. The filing of a lawsuit within 45 days of receipt of a Paragraph IV certification notice prevents the FDA from approving the ANDA until the earliest of 30 months after receipt of the Paragraph IV certification, expiration of the patent or a decision in the infringement case that is favorable to the ANDA applicant.

Market and data exclusivity provisions under the FDCA can delay the submission or the approval of certain drug applications for competing products, including generic drugs. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a New Chemical Entity. A drug is a New Chemical Entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the activity of the drug substance. During the exclusivity period, the FDA may not accept for review an ANDA or an NDA under Section 505(b)(2) of the FDCA, or an 505(b)(2) NDA, submitted by another company that references the previously approved drug. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a Paragraph IV certification.

The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application or supplement. Three-year exclusivity may be awarded for changes to a previously approved drug product, such as new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. The five-year and three-year exclusivities will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Biosimilars and Exclusivity

The 2010 Patient Protection and Affordable Care Act, or ACA, which was signed into law on March 23, 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. As of January 1, 2019, the FDA has approved 16 biosimilar products for use in the United States. No interchangeable biosimilars, as described below, have been approved. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars. Additional guidances are expected to be finalized by FDA in the near term.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity and potency. For the FDA to approve a biosimilar product as "interchangeable" with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and for products administered multiple times, that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such 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.

Patent Term Restoration and Extension

A patent claiming a new drug product or its method of use may be eligible for a limited patent term extension, also known as patent term restoration, under the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. Patent term extension is generally available only for drug products whose active ingredient has not previously been approved by the FDA. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of a marketing approval application, plus the time between the submission date of a marketing approval application and the ultimate approval date. Patent term extension cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office (USPTO) reviews and approves the application for any patent term extension in consultation with the FDA.

Orphan Drug Designation and Exclusivity

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, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an application for the product and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same product for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different indications. In particular, the concept of what constitutes a "same product" for purposes of orphan drug exclusivity is unclear in the context of gene therapies, and the FDA has issued draft guidance

suggesting minor variations in the construct of a gene therapy that lead to improvements in safety or efficacy may result in the determination that a drug is a "different product". If a product designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety or provides a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. This outcome is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent exclusivity in the United States and, if granted, provides for an additional six months of marketing protection to the term of any existing regulatory exclusivity or patent protection, including the non-patent and orphan drug exclusivity. This six-month exclusivity may be granted if an application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection covering the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve an ANDA or 505(b)(2) NDA that references the product. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which an ANDA or 505(b)(2) applicant submitted a paragraph IV certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by the proposed ANDA or 505(b)(2) product.

Review and Approval of Products in Europe and other Foreign Jurisdictions

In addition to regulations in the United States, a manufacturer is subject to a variety of regulations in foreign jurisdictions to the extent it chooses to conduct clinical trials or sell any products in those foreign countries. Even if a manufacturer obtains FDA approval of a product, it must still 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. To obtain regulatory approval of an investigational product in the European Union, a manufacturer must submit a marketing authorization application, or MAA, to the EMA. For other countries outside of the European Union, such as countries in Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, clinical trials are to be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Clinical Trial Approval in the European Union

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, an applicant must obtain approval from the competent national authority of the European Union Member State, or the EU Member State, in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the applicant may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new legislation aims at simplifying and streamlining the approval of clinical trials in the European Union. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one EU Member State will only be required to submit a single application for approval of a clinical trial to a reporting EU Member State. The Clinical Trials Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials. As of January 1, 2019, the website of the European Commission reported that the implementation of the Clinical Trials Regulation was dependent on the development of a fully functional clinical trials portal and database, which would be confirmed by an independent audit, and that the new legislation would come into effect six months after the European Commission publishes a notice of this confirmation.

Marketing Authorization

In the European Union, marketing authorizations for medicinal products may be obtained through different procedures founded on the same basic regulatory process. A marketing authorization may be granted only to an applicant established in the European Union. As in the United States, marketing authorization holders and manufacturers of approved medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the marketing authorizations.

Centralized Procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area, i.e. the European Union as well as Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for medicinal products produced by certain biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of certain diseases. It is optional for those products that are highly innovative or for which a centralized process is not in the interest of patients.

Specialized Procedures for Gene Therapies. The grant of marketing authorization in the European Union for gene therapy products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC includes specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety, and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Decentralized Procedure. The decentralized procedure provides for approval by one or more other concerned EU Member States of an assessment of an MAA conducted by one EU Member State, known as the reference EU Member State. In accordance with this procedure, an applicant submits an MAA to the reference EU Member State and the concerned EU Member States. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. Following receipt of a valid application, the reference EU Member State prepares a draft assessment and drafts of the related materials. The resulting assessment report is submitted to the concerned EU Member States which must decide whether to approve the assessment report and related materials.

If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States. Authorization in accordance with the decentralized procedure will result in authorization of the medicinal product only in the reference EU Member State and in the other concerned EU Member States.

Mutual Recognition Procedure. In accordance with the mutual recognition procedure, the sponsor applies for national marketing authorization in one EU Member State. Upon receipt of this authorization the sponsor can then seek the recognition of this authorization by other EU Member States.

Periods of Authorization and Renewals in the European Union

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the relevant EU Member State. To seek renewal, at least six months prior to expiration of the marketing authorization, the holder must provide the EMA or the EU Member State with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the relevant competent authority of the EU Member State decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any marketing authorization that is not followed by the marketing of the medicinal product on the EU market, in the case of the centralized procedure, or on the market of the EU Member State which delivered the marketing authorization, in the case of the decentralized procedure, within three years after authorization ceases to be valid.

Regulatory Data Exclusivity in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are shown to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be an innovative medicinal product so that the innovator gains the additional prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Orphan Drug Designation and Exclusivity in the European Union

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan medicinal product by the European Commission if its sponsor can establish that the product is intended for the diagnosis, prevention or treatment of: (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives the medicinal product is unlikely to be developed. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States and, in addition, a range of other benefits during the development and regulatory review process, including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all EU Member States and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Pediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the European Union, applicants must demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, approved by the Pediatric Committee of the EMA, or PDCO, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The PDCO may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA must determine that the applicant actually complied with the agreed studies and measures listed in each relevant PIP. If an applicant obtains a marketing authorization in all EU Member States, or a marketing authorization granted via the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom, or UK, voted in favor of leaving the European Union, which is commonly referred to as "Brexit". Thereafter, on March 29, 2017, the country formally notified the European Union of its intention to withdraw from the European Union. The process for withdrawal has been and remains uncertain and convoluted, with no withdrawal agreement between the government of the UK and the European Union concluded at this time. If no withdrawal agreement is reached by March 29, 2019, Brexit is currently scheduled to occur but without any transition mechanism in place. As the current regulatory framework for investigational medicines and approved products in the UK is derived from European Union directives and regulations, uncertainty regarding Brexit translates to uncertainty regarding the UK regulatory regime that will be applicable to our business following the scheduled March 29, 2019 Brexit effective date.

Pharmaceutical Insurance Coverage, Pricing and Reimbursement

In the United States and markets in many other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, the product. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage for a particular indication to specific products on an approved list, also known as a formulary, which might not include all of the approved products for such indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the studies required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered by payors to be medically necessary or cost effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Moreover, coverage policies and third-party reimbursement rates may change at any time.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of pharmaceutical products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including rebate programs, price controls, restrictions on reimbursement and requirements for substitution of generic products. For example, the Trump Administration has expressed an interest in authorizing and/or directing the Center for Medicare & Medicaid Services, or CMS, within HHS or other agencies of the U.S. government to negotiate prices for products covered by Medicare directly with pharmaceutical companies. If this were to occur, especially for AMD products, where a large portion of the patient population is elderly and is therefore covered by Medicare, there could be significant downward pressure on prices charged, not only for patients covered by Medicare, but also for patients covered by private insurers who may follow the government's lead on price. In addition, in May 2018, the Trump Administration announced a plan that would include several initiatives designed to lower drug prices. Additional similar proposals from HHS and CMS have followed.

At the state level, individual states are increasingly passing legislation and implementing 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, measures designed to encourage importation from other countries and bulk purchasing. In addition, regional health care 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 health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. Outside the United States, ensuring adequate coverage and payment for a product also involves challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require a clinical trial that compares the cost effectiveness of a product to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the

completion of additional cost effectiveness clinical studies. European Union member states may approve a specific price for a product or any of them may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union over the past decade. Reference pricing used by various European Union member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices.

In addition to initiatives specifically directed at lowering or containing prescription drug prices, legislative action in the United States at the national level has resulted in reduced funding levels for Medicare. For example, the Budget Control Act of 2011 led to aggregate reductions in Medicare payments to providers of up to 2% per fiscal year beginning in 2013 through 2024, and the American Taxpayer Relief Act of 2012 reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Any reduction in healthcare, including Medicare, funding may affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Moreover, the number of individuals covered by health insurance has a direct impact on the potential market for our product candidates, if approved. The ACA, passed in 2010, included the "individual mandate," which required most Americans to carry a minimal level of health insurance. Individuals who did not obtain required coverage were subjected to a penalty. The "individual mandate" was repealed as part of the Tax Cuts and Jobs Act of 2017, with the repeal becoming effective on January 1, 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. In addition, the Trump Administration has also taken executive actions that may impact the number of individuals in the United States that are covered by health insurance and the level of that coverage. For example, President Trump issued an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. In addition, CMS has proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, in June 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued the payments were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace and providers are not yet known.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health, or HITECH, Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute, which prohibits 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;

- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or collectively the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the CMS information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state anti–kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non–governmental third–party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws, such as the European Union's General Data Protection Regulation, or GDPR, also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Employees

As of January 31, 2019, we had 35 full-time employees, including a total of 5 employees with M.D. or Ph.D. degrees. Of our workforce, 16 employees are engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements.

Our Corporate Information

We were incorporated under the laws of the State of Delaware in 2007. Our principal executive offices are located at One Penn Plaza, 35th Floor, New York, NY 10119, and our telephone number is (212) 845–8200. Our Internet website is http://www.ophthotech.com.

Available Information

We make available free of charge through our website our Annual Report on Form 10–K, Quarterly Reports on Form 10–Q, Current Reports on Form 8–K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. You can find, copy and inspect information we file at the SEC's public reference room. You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at http://www.sec.gov. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report on Form 10–K.

Item 1A. Risk Factors.

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 1 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Business Plan, Financial Position and Need for Additional Capital

We are a development-stage company without any commercial products. The value of our company, therefore, is highly dependent on the success of our research and development efforts and the amount of our available cash. Our research and development programs, which are focused on novel therapies and technologies, carry significant scientific and other risks. If any of these programs are not successful, the value of your investment may decline.

We are a development-stage company without any approved products. Our growth prospects and the future value of our company are highly dependent on the progress of our ongoing clinical development programs for Zimura, our preclinical development programs for our HtrA1 inhibitors, our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidates for which we have an option from Penn and UFRF, and the activities being performed under our collaborative gene therapy sponsored research programs. Drug development is a highly uncertain undertaking and carries significant scientific and other risks.

We may encounter unforeseen difficulties, complications, delays, expenses and other known and unknown factors. We may never be successful in developing or commercializing any of our product candidates or other programs. There is a high rate of failure in early stage pharmaceutical research and development. Even if we have promising preclinical or clinical candidates, their development could fail at any time. Our failure could be due to unexpected scientific, safety or efficacy issues with our product candidates and other programs, invalid hypotheses regarding the molecular targets and mechanisms of action we choose to pursue or unexpected delays in our research and development programs resulting from applying the wrong criteria or experimental systems and procedures to our programs or lack of experience, with the possible result that none of our product candidates or other programs result in the development of marketable products. We have not yet demonstrated our ability to successfully complete the development of a pharmaceutical product, including completion of large-scale, pivotal clinical trials with safety and efficacy data sufficient to obtain marketing approval or activities necessary to apply for and obtain marketing approval, including the qualification of a commercial manufacturer through a pre-approval inspection with regulatory authorities. If successful in developing and obtaining marketing approval of one of our product candidates, we would need to transition from a company with a product development focus to a company capable of supporting commercial activities. We may not be successful in such a transition, as our company has never conducted the sales, marketing and distribution activities necessary for successful product commercialization.

Because the value of our company is largely based on the prospects for our research and development programs and their potential to result in therapies capable of achieving marketing approval and generating future revenues, any failure, delay or setback for these programs will likely have a negative impact on the value of your investment. For example, we expect to receive initial top-line data from OPH2003, our ongoing Phase 2b clinical trial of Zimura for the treatment of GA secondary to dry AMD, during the fourth quarter of 2019. If such data are negative or do not support further development of Zimura in GA, or if we are to cease development of Zimura in STGD1 as a result of such data or for other reasons, the value of our common stock could be negatively impacted. In addition, because a number of our product candidates are in an early, preclinical stage, even if we are successful in advancing the research and development of those product candidates, the value of our common stock may not rise in a meaningful way, which could affect our ability to raise additional finances. As we continue to invest in these research and development programs to generate data to support further development, the amount of our available cash will continue to decline until such time as we raise additional finances.

We have a history of significant operating losses. We expect to continue to incur losses until such time, if ever, that we successfully commercialize our product candidates and may never achieve or maintain profitability.

Since inception, we have experienced significant cash outflows in funding our operations. To date, we have not generated any revenues from commercial product sales and have financed our operations primarily through private placements of our preferred stock, venture debt borrowings, funds received under our prior Fovista royalty purchase and sale agreement with Novo Holdings A/S, our initial public offering, which we closed in September 2013, our follow-on public offering, which we closed in February 2014, funds we received under our prior Fovista licensing and commercialization agreement with

Novartis Pharma, AG, and funds we received in connection with our acquisition of Inception 4 in October 2018. As of December 31, 2018, we had an accumulated deficit of $421.7 million. Although we have recorded net income in the amount of $63.1 million for the year ended December 31, 2018 on account of the gain that we recognized upon the extinguishment of the royalty purchase liability under our prior Fovista royalty purchase and sale agreement with Novo Holdings A/S, we incurred an operating loss of $65.3 million for such year and expect to continue to incur significant operating losses for the foreseeable future.

Our product candidate Zimura is in clinical development, our HtrA1 inhibitor program, our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling activities are each in preclinical development, and we are funding sponsored research programs that are ongoing at UMMS and Penn. We expect our research and development expenses to increase as we pursue our research and development programs, as currently planned. We could also incur additional research and development expenses as we evaluate and potentially in-license or acquire, and undertake development of additional product candidates, including any promising product candidates that emerge from our collaborative gene therapy sponsored research programs. Furthermore, if we successfully develop and obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. We are party to agreements with Archemix with respect to Zimura, the former equityholders of Inception 4 with respect to our HtrA1 inhibitor program and UFRF and Penn with respect to our RHO-adRP gene therapy product candidate, in each case, that impose significant milestone payment obligations on us in connection with our achievement of specified clinical, regulatory and commercial milestones with respect to these product candidates or programs, as well as certain royalties on net sales with respect to our RHO-adRP gene therapy product candidate. It is likely that any future in-licensing or acquisition agreements that we enter into with respect to additional products, product candidates or technologies, including any definitive license agreement for the BEST1 product candidates for which we hold an option from Penn and UFRF, would include similar obligations.

We expect that we will continue to incur significant expenses as we:

- continue the clinical development of Zimura as currently planned, including, if either of our ongoing trials for Zimura support it, by pursuing additional development;
- continue the preclinical and, potentially, clinical development of our HtrA1 inhibitor program, our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling activities;
- pursue our collaborative gene therapy sponsored research programs;
- in-license or acquire the rights to, and pursue the development of, other products, product candidates or technologies;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, manufacturing, quality control, quality assurance and scientific personnel, especially as we increase our internal gene therapy capabilities or if we are successful in progressing the preclinical or clinical development of any of our product candidates or in acquiring or in-licensing rights to additional products, product candidates or technologies;
- seek marketing approval for any product candidates that successfully complete clinical trials;
- expand our outsourced manufacturing activities or establish commercial operations or sales, marketing and distribution capabilities, if we receive, or expect to receive, marketing approval for any of our product candidates; and
- expand our general and administrative functions to support future growth of the company.

Our ability to become and remain profitable depends on our ability to generate revenue in excess of our expenses. Our ability to generate revenues from product sales is dependent on our obtaining marketing approval for and commercializing our product candidates or any product candidates we may in-license or acquire. We may be unsuccessful in our efforts to develop and commercialize product candidates or in our efforts to in-license or acquire additional product candidates. Even if we succeed in developing and commercializing one or more of our product candidates, we may never achieve sufficient sales revenue to achieve or maintain profitability. See “Risks Related to Product Development and Commercialization” for a further discussion of the risks we face in successfully developing and commercializing our product candidates and achieving profitability.

We expect we will require substantial, additional funding in order to complete the activities necessary to develop and commercialize one or more of our product candidates. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts. We may require additional funding beyond what we currently expect.

As of December 31, 2018, we had cash and cash equivalents of $131.2 million. We believe that our cash and cash equivalents will be sufficient to fund our operations and capital expenditure requirements as currently planned for at least the next 12 months. This estimate does not reflect any additional expenditures resulting from additional sponsored research or the in-licensing or acquisition of additional product candidates or technologies or associated development that we may pursue following any such transactions. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

Although the future development of our product candidates is highly uncertain, we expect we will require substantial, additional funding in order to complete the activities necessary to develop and commercialize one or more of our product candidates. We expect the development of our product candidates will continue for at least the next several years. At this time, we cannot reasonably estimate the remaining costs necessary to complete development, to complete process development and manufacturing scale-up and validation activities and to potentially seek marketing approval with respect to our product candidates.

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

- the scope, progress, costs and results of our ongoing Zimura clinical programs, as well as any additional clinical trials we undertake to obtain data sufficient to seek marketing approval for Zimura in any indication;
- the scope, progress, costs and results of our efforts to develop our HtrA1 inhibitor program, including formulation development and other preclinical development activities;
- the scope, progress, costs and results of our efforts to develop our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidate for which are planning to commence IND-enabling activities, including activities to establish manufacturing capabilities and preclinical testing to enable us to file INDs for these product candidates;
- the costs and timing of process development, manufacturing scale-up and validation activities and stability studies associated with our product candidates;
- the extent to which we in-license or acquire rights to, and undertake research or development of, additional products, product candidates or technologies, including any product candidates or other technologies we may evaluate as part of our collaborative gene therapy sponsored research programs;
- the amount of any upfront, milestone payments and other financial obligations associated with the in-license or acquisition of other product candidates;
- the scope, progress, results and costs of preclinical development and/or clinical trials for any other product candidates that we may develop;
- our ability to establish collaborations on favorable terms, if at all;
- the costs, timing and outcome of regulatory filings and reviews of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending intellectual property-related claims;
- the timing, scope and cost of commercialization activities for any of our product candidates if we receive, or expect to receive, marketing approval for a product candidate; and
- subject to receipt of marketing approval, net revenue received from commercial sales of any of our product candidates, after milestone payments and royalty payments that we would be obligated to make.

We do not have any committed external source of funds. Our ability to raise adequate additional financing when needed, and on terms acceptable to us, will depend on many factors. These factors include investors' perceptions of the potential success of our ongoing business activities, including the development of our product candidates and other programs, and the potential future growth of our business. Additionally, these factors include general market conditions that also affect other companies. These factors may make raising capital difficult, and may result in us accepting terms that are unfavorable to us, especially if we are in need of financing at the particular time. The size of our company and our status as a company listed on The Nasdaq Stock Market, or Nasdaq, may also limit our ability to raise financing. For example, our ability to raise adequate financing through a public offering may be limited by market conditions and SEC rules based on our current market capitalization. Nasdaq listing rules also generally limit the number of shares we may issue in a private placement to a number less than 20% of the number of shares of our common stock outstanding immediately prior to the transaction, unless we obtain shareholder approval, which can be expensive and time-consuming and can add risk to our ability to complete the financing transaction. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate the development of our product candidates, our collaborative gene therapy sponsored research programs, or our future commercialization efforts.

In addition, we may require additional funding beyond what we currently expect due to unforeseen or other reasons. For example, our costs may exceed our expectations if we experience any unforeseen issue in our ongoing clinical trials, such as delays in enrollment or issues with the availability of drug supply, or in our preclinical development programs, such as inability to develop formulations or if we experience issues with manufacturing, or if we further expand the scope of our clinical trials, preclinical development programs or collaborative gene therapy sponsored research programs. Our costs may also exceed our expectations for other reasons, for example, if we are required by the FDA, the EMA or regulatory authorities in other jurisdictions to perform clinical or nonclinical trials or other studies in addition to those we currently expect to conduct, if we experience issues with process development, establishing or scaling-up of manufacturing activities or activities to enable and qualify second source suppliers, or if we decide to increase preclinical and clinical research and development activities or build internal research capabilities or pursue internal research efforts. As a result, we may need or may seek to obtain additional funding for our continuing operations sooner or in greater amounts than expected.

Our need for additional financing may continue even if we are able to successfully develop one or more of our product candidates. Our future commercial revenues, if any, will be derived from sales of such product candidates, which may not be available for at least several years following completion of successful product development, if at all. In addition, if approved, our product candidates may not achieve commercial success. Even if those products are successful and we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Under most, if not all, of the foregoing circumstances, we may need to obtain substantial additional financing to achieve our business objectives.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, when we can generate substantial product revenues, we may need or may seek to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our existing stockholders' ownership interests would be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect our existing stockholders' rights as common stockholders. The dilutive effect of future capital raises may be substantial, depending on the price of our common stock at the time of such capital raise, with a lower stock price translating to greater dilution for existing stockholders. 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. In addition, we may issue equity securities as consideration for further business development transactions, which may also dilute our existing stockholders' ownership interests.

For example, under the Inception 4 Merger Agreement pursuant to which we acquired Inception 4 and our HtrA1 inhibitor program, we issued 5,174,727 shares of our common stock as up-front consideration to the former equityholders of Inception 4. This issuance might have resulted in the dilution of our existing stockholders' ownership interests. The Inception 4 Merger Agreement also requires us to make payments to the former equityholders of Inception 4 upon the achievement of certain clinical and regulatory milestones, subject to the terms and conditions set forth in the Inception 4 Merger Agreement. Those milestone payments will be in the form of shares of our common stock, calculated based on the price of our common stock over a five-trading day period preceding the achievement of the relevant milestone, unless and until the issuance of such shares would, together with all other shares issued in connection with the Inception 4 Merger, exceed an overall maximum limit of approximately 7.2 million shares, which is equal to 19.9% of the number of issued and outstanding shares of our common

stock as of the close of business on the business day prior to the closing date, and will be payable in cash thereafter. The issuance of additional shares as milestone consideration may dilute our existing stockholders.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, products 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 grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

In August 2018, we entered into a Sales Agreement with Cowen and Company, LLC, or Cowen, as agent, pursuant to which we may offer and sell shares of our common stock for aggregate gross sale proceeds of up to $50.0 million from time to time through Cowen under an "at-the-market" offering program, subject to the terms and conditions described in the sale agreement and SEC rules and regulations. We have not yet issued and sold any shares of common stock under our "at-the-market" offering program. If we make sales under our "at-the-market" offering program, the sales could dilute our stockholders, reduce the trading price of our common stock or impede our ability to raise future capital.

Our strategy of obtaining rights to products, product candidates or technologies for the treatment of ophthalmic diseases through in-licenses and acquisitions may not be successful.

An element of our strategy has been to expand our pipeline through potentially in-licensing or acquiring the rights to products, product candidates or technologies that would complement our strategic goals as well as other compelling ophthalmology opportunities. Although over the course of 2018 we completed multiple acquisition, in-license, exclusive option and sponsored research arrangements, we expect to continue to evaluate opportunities to potentially obtain rights to additional gene therapy and therapeutic product candidates on a selective basis. Because we expect generally that we will not engage directly in internal early stage research and drug discovery efforts, the future growth of our business beyond our current product portfolio will depend on our ability to obtain those rights to additional gene therapy and therapeutic product candidates, including any promising product candidates that may emerge from our collaborative gene therapy sponsored research programs. We may also continue to consider other alternatives, including mergers or other transactions involving our company as a whole or other collaboration transactions. Our business development efforts may fail to result in our acquiring rights to additional products, product candidates or technologies, or may result in our consummating transactions with which you do not agree.

We may be unable to in-license or acquire the rights to any such products, product candidates or technologies from third parties for several reasons. The success of this strategy depends partly upon our ability to identify, select and acquire or in-license promising product candidates and technologies. We may be unable to identify suitable products, product candidates or technologies within our area of focus. Although we are planning to target opportunities where we believe third-party funding for specific programs or technologies may be available, funding may not in fact be available for any number of reasons. The process of proposing, negotiating and implementing a license or acquisition of a product candidate is lengthy and complex.

The in-licensing and acquisition of pharmaceutical products is an area characterized by intense competition, and a number of companies (both more established and early stage biotechnology companies) are also pursuing strategies to in-license or acquire products, product candidates or technologies that we may consider attractive. We believe that other companies may be particularly active in pursuing opportunities to in-license or acquire promising gene therapy opportunities. More established companies may have a competitive advantage over us due to their size, cash resources and greater research, preclinical or clinical development or commercialization capabilities, while earlier stage companies may be more aggressive or have a higher risk tolerance. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to in-license or acquire the rights to the relevant product, product candidate or technology on terms that would allow us to make an appropriate return on our investment. Moreover, we may devote resources to potential acquisitions or in-licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts or we may incorrectly judge the value of an acquired or in-licensed product candidate or technology.

Further, any product candidate that we acquire would most likely require additional development efforts prior to commercial sale, including extensive clinical testing and approval by the FDA, and applicable foreign regulatory authorities. All product candidates are prone to risks of failure typical of pharmaceutical product development, including the possibility that a product candidate would not be shown to be sufficiently safe and effective for approval by regulatory authorities.

If we are unable to successfully obtain rights to suitable products, product candidates or technologies, our business, financial condition and prospects for growth could suffer. In addition, acquisitions and in-licensing arrangements for product candidates and technologies are inherently risky, and ultimately, if we do not complete an announced acquisition or license transaction or integrate an acquired or licensed product or technology successfully and in a timely manner, we may not realize

the benefits of the acquisition or license to the extent anticipated and the perception of the effectiveness of our management team and our company may suffer in the marketplace. In addition, even if we are able to successfully identify, negotiate and execute one or more transactions to acquire or in-license new products, product candidates or technologies, our expenses and short-term costs may increase materially and adversely affect our liquidity.

In addition, acquisitions and in-licenses may entail numerous operational, financial and legal risks, including:

- exposure to known and unknown liabilities, including possible intellectual property infringement claims, violations of laws, tax liabilities and commercial disputes;
- incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions;
- higher than expected acquisition and integration costs;
- difficulty in combining the operations and personnel of any acquired businesses with our operations and personnel;
- inability to maintain uniform standards, controls, procedures and policies;
- restructuring charges related to eliminating redundancies or disposing of assets as part of any such combination;
- large write-offs and difficulties in assessing the relative percentages of in-process research and development expense that can be immediately written off as compare to the amount that must be amortized over the appropriate life of the asset;
- increased amortization expenses or, in the event that we write-down the value of acquired assets, impairment losses;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership;
- inability to retain personnel, key customers, distributors, vendors and other business partners integral to an in-licensed or acquired product candidate or technology;
- potential failure of the due diligence process to identify significant problems, liabilities or other shortcomings or challenges of an acquired or licensed product candidate or technology, including, without limitation, problems, liabilities or other shortcomings or challenges with respect to intellectual property, product quality, revenue recognition or other accounting practices, partner disputes or issues and other legal and financial contingencies and known and unknown liabilities; and
- entry into therapeutic modalities, indications or markets in which we have no or limited direct prior development or commercial experience and where competitors in such markets have stronger market positions.

We may not successfully integrate our newly acquired HtrA1 inhibitor program.

Our acquisition of Inception 4 involves the integration of Inception 4's HtrA1 inhibitor program and technology with our existing operations and programs, and there are uncertainties inherent in such integration. We have devoted and will continue to devote significant management attention and resources to the Inception 4 integration and to the further development of our HtrA1 inhibitor program. Delays, unexpected difficulties in the integration process or failure to retain key consultants or other resources previously used by Inception 4 could adversely affect the development of our HtrA1 inhibitor program, our business and our financial condition. Even if we are able to conduct the integration successfully, we may not fully realize the benefits of the Inception 4 acquisition within a reasonable period of time. In addition, although we conducted a diligence process in connection with the acquisition of Inception 4, we may not yet be aware of all factors regarding Inception 4 that could produce unintended and unexpected consequences for us. These factors could cause us to incur potentially material liabilities.

We and certain of our current and former executive officers have been named as defendants in lawsuits that could result in substantial costs and divert management's attention.

We and certain of our current and former executive officers have been named as defendants in a purported consolidated putative class action lawsuit initiated in 2017 that generally alleges that we and certain of our officers violated Sections 10(b) and/or 20(a) of the Exchange Act and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements concerning the results of our Phase 2b trial and the prospects of our Phase 3 trials for Fovista in combination with anti-VEGF agents for the treatment of wet AMD. The members of our board of directors have also been named as defendants in a shareholder derivative action initiated in February 2018, which generally alleges that the defendants breached their fiduciary duties to our company by adopting a compensation plan that overcompensates the non-employee members of the board relative to the boards of companies of comparable market capitalization and size. The current and former members of our board of directors and certain current and former officers have also been named as defendants in a shareholder derivative action initiated in August 2018, which generally alleges that the defendants breached their fiduciary duties to our company by failing to oversee our business during the period of the Phase 2b and Phase 3 clinical trials of Fovista. These complaints seek equitable and/or injunctive relief, unspecified damages, attorneys' fees, and other costs. We and the defendants deny any and all allegations of wrongdoing and intend to vigorously defend against these lawsuits. We are unable, however, to predict the outcome of these matters at this time. Moreover, any conclusion of these matters in a manner adverse to us and for which we incur substantial costs or damages not covered by our directors' and officers' liability insurance would have a material adverse effect on our financial condition and business. In addition, the litigation could adversely impact our reputation and divert management and our board of directors' attention and resources from other priorities, including the execution of our business plan and strategies that are important to our ability to grow our business, any of which could have a material adverse effect on our business. Additional similar lawsuits may be filed.

The comprehensive tax reform bill passed in December 2017 could adversely affect our business and financial condition.

On December 22, 2017, United States President Donald J. Trump signed into law new legislation that significantly revised the Internal Revenue Code of 1986, as amended. The newly enacted federal income tax law, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modification or repeal of many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. The United States Department of Treasury and the Internal Revenue Service are continuing to issue new guidance and interpretations of various provisions of the new tax law. In addition, it is uncertain how various states will respond to the newly enacted federal tax law. The impact of this new tax law on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

Risks Related to Product Development and Commercialization

Companies in our industry face a wide range of challenging activities, each of which entails separate, and in many cases substantial, risk.

The long-term success of our company, and our ability to become profitable as a biopharmaceutical company, will require us to be successful in a range of challenging activities, including:

- designing, conducting and successfully completing preclinical research and development activities, including preclinical efficacy and IND-enabling studies, for our product candidates or product candidates we are interested in in-licensing or acquiring, including those that we may evaluate as part of our collaborative gene therapy sponsored research programs;
- designing, conducting and completing clinical trials for our product candidates;
- obtaining favorable results from required clinical trials, including for each ophthalmic product candidate, favorable results from two adequate and well-controlled pivotal clinical trials in the relevant indication;
- applying for and receiving marketing approvals from applicable regulatory authorities for the marketing and sale of our product candidates;

- making arrangements with third-party manufacturers, receiving regulatory approval of our manufacturing processes and our third-party manufacturers' facilities and ensuring adequate supply of drug product and starting materials used for the manufacture of drug product;
- establishing sales, marketing and distribution capabilities, either internally or through collaborations or other arrangements, to effectively market and sell our product candidates;
- achieving acceptance of the product candidate, if and when approved, by patients, the medical community and third-party payors;
- if our product candidates are approved, obtaining from governmental and third-party payors adequate coverage and reimbursement for our product candidates and, to the extent applicable, associated injection procedures conducted by treating physicians;
- effectively competing with other therapies, including the existing standard of care, and other forms of drug delivery;
- maintaining a continued acceptable safety profile of the product candidate during development and following approval;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity, including under the Orphan Drug Act and the Hatch-Waxman Amendments to the FDCA, if we choose to seek such protections for any of our product candidates;
- protecting and enforcing our rights in our intellectual property portfolio; and
- complying with all applicable regulatory requirements, including FDA Good Laboratory Practices, or GLP, FDA Good Clinical Practices, or GCP, current Good Manufacturing Practices, or cGMP, and standards, rules and regulations governing promotional and other marketing activities.

Each of these activities has associated risks, many of which are detailed below and throughout this "Risk Factors" section. We may never succeed in these activities and, even if we do, may never generate revenues from product sales that are significant enough to achieve commercial success and profitability. Our failure to be commercially successful and profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or continue our operations. A decrease in the value of our company would also cause our stockholders to lose all or part of their investment.

Drug development is a highly uncertain undertaking. Our research and development efforts may not be successful or may be delayed for any number of reasons, in which case potential marketing approval or commercialization of our product candidates could be prevented or delayed.

Before obtaining approval from regulatory authorities for the sale of any product candidate, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Prior to initiating clinical trials, a sponsor must complete extensive preclinical testing of a product candidate, including, in most cases, preclinical efficacy experiments as well as IND-enabling toxicology studies. Early stage research, such as the research we are sponsoring with UMMS, may never yield a product candidate for preclinical or clinical development. Early stage research experiments and preclinical studies may fail at any point for any number of reasons, and even if completed, may be time-consuming and expensive. As a result of these risks, a potentially promising product candidate may never be tested in humans. Once it commences, clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, our pivotal Phase 3 Fovista program for the treatment of wet AMD failed to produce positive safety and efficacy data that support the use of Fovista in wet AMD, despite the results from preclinical testing and earlier clinical trials of Fovista. Furthermore, our Phase 2a OPH2007 trial of Zimura in wet AMD did not replicate the results of our Phase 1/2a OPH2000 trial, following which we decided not to proceed with further development of Zimura in wet AMD at this point. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We may experience numerous unforeseen events during drug development that could delay or prevent our ability to receive marketing approval or commercialize our product candidates. These risks include, but are not limited to, the following:

- we may not be able to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation of clinical studies for any preclinical product candidates that we are developing or may wish to in-license or acquire;
- regulators or institutional review boards may not agree with our study design, including our selection of endpoints, or may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective contract research organizations or clinical trial sites, especially in cases where we are working with contract research organizations or clinical trial sites we have not worked with previously;
- our contract research organizations, clinical trial sites, contract manufacturers, providers of starting materials and packagers and analytical testing service providers may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we, through our clinical trial sites, may not be able to locate and enroll a sufficient number of eligible patients to participate in our clinical trials as required by the FDA or similar regulatory authorities outside the United States, especially in our clinical trials for orphan or other rare diseases;
- we may decide, or regulators or institutional review boards may require us, to suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements, including GCPs, or a finding that the participants are being exposed to unacceptable health risks;
- as there are no therapies approved for GA, Stargardt disease, RHO-adRP or Best disease in either the United States or the European Union, the regulatory pathway for product candidates in these indications, including the selection of the primary efficacy endpoint for a pivotal clinical trial, is highly uncertain;
- there may be changes in regulatory requirements and guidance or we may have changes in trial design that require amending or submitting new clinical trial protocols;
- there may be changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- we may decide, or regulators may require us, to conduct additional clinical trials beyond those we currently contemplate or to abandon product development programs;
- the number of patients required for clinical trials of our product candidates to demonstrate statistically significant results 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. These risks may be heightened for clinical trials in orphan diseases, for which the natural history of the disease is less understood, making it more difficult to predict the drug effect required to adequately demonstrate efficacy, and because there are fewer affected individuals available to participate in clinical trials;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- we or our contract manufacturers may be unable to develop a viable manufacturing process for any product candidates that we are developing;
- the supply or quality of our product candidates or other materials necessary to conduct preclinical development and clinical trials of our product candidates may be insufficient or inadequate or we may face delays in the manufacture and supply of our product candidates as a result of a decision to transfer manufacturing between contract manufacturers or on account of interruptions in our supply chain, including in relation to the procurement of starting materials, such as plasmids used for the manufacture of our gene therapy product candidates, and the packaging and distribution or import/export of clinical materials; and

- we may face delays in the manufacture and supply of any product candidates we are investigating in our collaborative gene therapy sponsored research programs as a result of our inability to establish manufacturing capabilities or processes or to obtain necessary starting materials, such as plasmids.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we 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:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use limitations, 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.

Despite our current development plans and ongoing efforts, we may not complete any of our ongoing or planned clinical trials or other clinical trials for our product candidates. The timing of the completion of, and the availability of results from, clinical trials is difficult to predict. We do not know whether clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Furthermore, our development plans may change based on feedback we may receive from regulatory authorities throughout the development process. If we experience delays in manufacturing, testing or marketing approvals, our product development costs would increase. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Our development of Zimura is based on a novel mechanism of action that is unproven and poses a number of scientific and other risks, and we may not be successful in developing Zimura in the indications we are pursuing. Our ongoing and any future clinical trials for Zimura may not provide sufficient safety and efficacy data to support future development efforts or seeking and obtaining marketing approval.

We are targeting GA, an advanced form of dry AMD, and STGD1 with Zimura. The causes of AMD are not completely understood. In addition to advanced age, there are environmental and genetic risk factors that contribute to the development of AMD including ocular pigmentation, dietary factors, a positive family history for AMD, high blood pressure and smoking. Although we believe there is a scientific rationale for pursuing the development of inhibitors for selective molecular targets, including complement C5, as potential pharmaceutical treatments for AMD, this approach may not prove successful for treating AMD in a clinically meaningful way. Similarly, although there is non-clinical scientific literature supporting the potential use of inhibitors of the complement system for the treatment of STGD1, this approach may not prove clinically successful as well.

Zimura is designed to inhibit complement C5. There are no FDA or EMA approved products that utilize C5 inhibition as a mechanism of action to treat GA or STGD1, and this mechanism of action may not prove safe and effective for these diseases. Moreover, the failure of prior clinical trials evaluating complement inhibition in GA, including a competitor's two Phase 3 clinical trials evaluating an investigational anti-complement factor D antibody administered via intravitreal injections, a second competitor's Phase 2 clinical trial evaluating an investigational anti-C5 antibody administered via intravitreal injections and a third competitor's Phase 2 clinical trial evaluating an anti-C5 antibody administered systemically, may call into question the hypothesis underlying the use of a complement inhibitor as a method for treating GA.

We have only very limited data from a small, uncontrolled clinical trial regarding the safety and efficacy of Zimura as a monotherapy for the treatment of GA, and we have no human clinical data regarding the safety and efficacy of Zimura as a treatment for STGD1. Our prior Zimura trials were not powered to demonstrate the efficacy of Zimura therapy with statistical significance. Our ongoing and any future clinical trials for Zimura may fail to demonstrate sufficient safety or efficacy to justify further development or to ultimately seek or obtain marketing approval. Any negative results from our ongoing or any

future clinical trials for Zimura, including from our OPH2003 trial for which we expect initial top-line data to be available during the fourth quarter of 2019, could adversely affect our business and the value of your investment in our company.

The statistical analysis of a clinical trial outcome is primarily determined based on three factors: variability in the measured endpoint among the patient population, the magnitude of the drug effect observed in relation to that variability and the number of patients from whom data is collected in the clinical trial. Given that we have limited data regarding the effect of Zimura in GA, we determined the size of the OPH2003 trial in GA based on our best estimates of the size of trial required to demonstrate a potential clinical benefit for Zimura. This estimate incorporates our assumptions regarding the potential performance of Zimura in this indication based in part on available third-party clinical trial data and our statistical analysis of this data, as well as our assumptions regarding the number of patients that will continue to participate in the trial through the 12-month timepoint. In addition, although we initially determined the size of the OPH2005 trial in STGD1 based on the number of patients with STGD1 that we believed could potentially be enrolled within a reasonable period of time, we decided to cease patient enrollment during the first quarter of 2019 in light of the 18-month endpoint and our goal of providing initial top-line data from this trial by the end of 2020. As STGD1 is an orphan indication, to our knowledge there is only very limited natural history data currently available regarding the variability for our planned primary efficacy endpoint in the STGD1 patient population we enrolled in this trial. Moreover, because both GA and Stargardt disease are degenerative diseases, and in many cases, the rate of degeneration is slow, and because we are seeking to slow the progression of degeneration with Zimura, and not necessarily to reverse prior degeneration or restore visual function, patients participating in our trials may not perceive a benefit from continuing to participate and therefore may drop out of the trial. Although we and the investigators participating in our trials and their staff take efforts to encourage continued patient participation, the drop-out rate for our Zimura trials may exceed our expectations. A higher than expected drop-out rate would reduce the number of patients from whom data is available for analyzing the primary endpoint for these trials. Given the information above, these trials could be underpowered to demonstrate a potential clinical benefit for Zimura in these indications.

Furthermore, our recently completed OPH2007 clinical trial evaluated, and our current Zimura clinical trials are evaluating, Zimura dosing regimens that we have not studied extensively, which may increase the risk that patients in these trials experience adverse events and/or serious adverse events (either ocular, systemic or both) that we have not observed or at rates that we have not observed in prior trials. Although we did not observe adverse events or serious adverse events attributable to the drug product in our OPH2007 trial, those adverse events and/or serious adverse events may manifest in our current Zimura clinical trials. For a further discussion of the safety risks in our trials, see the risk factor herein entitled "*If serious adverse or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of such product candidates.*"

Our development of our HtrA1 inhibitor program is also based on a novel mechanism of action that is unproven and poses a number of scientific and other risks. We may not be able to successfully formulate a product candidate from our HtrA1 inhibitors.

Our HtrA1 inhibitor program is in preclinical development. There are no FDA or EMA approved products that utilize HtrA1 inhibition as a mechanism of action for treating ophthalmic diseases, including GA and other age-related retinal diseases for which we may develop our HtrA1 inhibitor program, such as wet AMD and IPCV, and this mechanism of action may not prove safe and effective for these diseases. We made the decision to acquire this program based on our interpretation of the scientific literature and rationale for this potential target that suggest an association between HtrA1 and the risk for AMD, as well as a limited set of preclinical data generated by Inception 4 prior to the acquisition. We note, however, the *HtrA1* gene is in the same region of the 10q26 chromosome as the *age-related maculopathy susceptibility 2*, or *ARMS2*, gene. The *ARMS2* and *HtrA1* genes are linked, and variants in, or expression of, the *ARMS2* gene may also be associated with the risk for AMD. The risk for AMD associated with *ARMS2* may ultimately prove to be greater than the risk associated with *HtrA1*. In addition, even though genetic and histologic findings correlate HtrA1 with AMD, the development and progression of AMD may not be affected by HtrA1. Our assumption that targeting inhibition of HtrA1 as a method of treating AMD may be incorrect, which would likely adversely affect the value of our HtrA1 inhibitor program and its continued development.

Before we can commence IND-enabling studies for our HtrA1 inhibitor program, we need to conduct pre-formulation and formulation studies with our lead compounds in this program to determine whether we can formulate a product candidate for intravitreal administration that is safe to advance into preclinical studies and, depending on the outcome of such studies, into clinical trials. As part of this work, we need to determine which inactive formulation components should be used in the preparation of the product candidate, and derive a preparation that includes an adequate amount of drug substance with the necessary inactive ingredients to achieve the desired safety profile for intravitreal injection into the eye while providing for sufficient pharmacological activity. Formulation development is inherently uncertain, and it is possible we may not be able to formulate any of our lead compounds into a preparation that is safe to advance into preclinical studies or clinical trials in the

eye or that provides sufficient pharmacological activity, which would hinder our ability to pursue development of this program. Formulation development can be time-consuming and our anticipated timelines for the development of this program may be delayed.

Gene therapy is an emerging field of drug development that poses many scientific and other risks. Also, we have only limited experience in gene therapy research and manufacturing and no experience in gene therapy clinical development. Our lack of experience may limit our ability to be successful or may delay our development efforts.

Gene therapy is an emerging field of drug development with only one gene replacement therapy having received FDA approval to date. Our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidates for which we hold an option from Penn and UFRF, as well as the "minigene" therapy approach and novel gene delivery methods we are evaluating in our sponsored research programs with UMMS, are in particularly early-stages of research and development. Even with promising preclinical efficacy data, there will remain several areas of drug development risk, including translational science, manufacturing materials and processes, safety concerns, regulatory pathway, clinical trial design and the approach to ocular gene therapy administration through either subretinal surgery or intravitreal delivery, which will likely pose particular uncertainty given the relatively limited development history for gene therapies. For example, the current construct for the BEST1 gene therapy product candidates for which we have an option from Penn and UFRF has been tested in an autosomal recessive canine bestrophinopathy model. A majority of humans with Best disease, however, have the autosomal dominant form of the disease, and we intend to develop the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling studies for the autosomal dominant form of Best disease and potentially other bestrophinopathies. The approach to treating this form of the disease with a construct previously studied in an autosomal recessive canine disease model may ultimately prove ineffective. In addition to the foregoing, because gene therapy is an emerging field of drug development and we have limited experience with gene therapies, we may encounter unexpected difficulties and challenges.

We have particularly focused on adeno-associated virus, or AAV, gene therapy, as AAV vectors are relatively specific to retinal cells and their safety profile in humans is relatively well-documented as compared to other delivery vehicles and gene therapy technologies currently in development. However, AAV has a number of drawbacks, including its small packaging capacity (an AAV vector can hold only up to approximately 4,700 base pairs of DNA, whereas the genes for a number of IRDs, such as Stargardt disease, exceed that size). Although AAV is the most commonly used vector in ocular gene therapy today, other vector forms, such as retroviral or lentiviral and non-viral based vectors, or gene editing approaches may prove to be safer and more effective.

Although we believe gene therapy is a promising area for ophthalmic drug development, our gene therapy research and development experience is limited to only a few personnel hired to supervise outside vendors. In pursuing this new area, we are starting to establish our gene therapy technical capabilities, including translational, manufacturing, process development, and other capabilities, but we will need to build those capabilities to a more significant level. We will either need to hire internally for these capabilities or establish them through outside service providers. We believe that gene therapy is an area of significant investment by biotechnology and pharmaceutical companies and that there may be a scarcity of talent available to us in these areas. If we are not able to establish our own internal or outsourced gene therapy capabilities to a more significant level, we may not be able to develop our RHO-adRP product candidate, the BEST1 gene therapy product candidates for which we hold an option from Penn and UFRF or other promising product candidates that emerge from our collaborative gene therapy sponsored research programs, which would limit our prospects for future growth.

For a further discussion of the risks associated with the manufacturing of gene therapy products, see the risk factor herein entitled "*The manufacture of gene therapy products is complex with a number of scientific and technical risks, some of which are common to the manufacture of drugs and biologics and others are unique to the manufacture of gene therapies. We have limited experience with gene therapy manufacturing and are dependent on our third-party contract manufacturers and sole source suppliers*".

If serious adverse or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of such product candidates.

If any of our product candidates are associated with serious adverse events or undesirable side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause side effects that prevented further development of the compound.

In particular, we have limited data regarding the safety, tolerability and efficacy of Zimura administered for the treatment of GA and no data regarding the safety, tolerability and efficacy of Zimura administered for the treatment of STGD1. In our completed clinical trials for Zimura, we have observed only a single adverse event, mild subcapsular cataract, from our OPH2000 trial, assessed to be drug-related by participating investigators. We have no human data regarding our HtrA1 inhibitor program, our RHO-adRP gene therapy product candidate or the BEST1 gene therapy product candidates for which we hold an option from Penn and UFRF.

Our clinical trials for Zimura involve dosing regimens that we have not studied extensively, which may increase the risk that patients in these trials experience adverse events and/or serious adverse events (either ocular, systemic or both) that we have not observed or at rates that we have not observed in prior trials. In addition, our clinical trials for Zimura will involve multiple intravitreal injections over an extended period of time and, as such, may involve risks regarding multiple and chronic intravitreal injections. For these reasons, there may be, among others, an increase in the rates of intraocular infections, or endophthalmitis, intraocular pressure, glaucoma, retinal tears, cataracts, retinal detachment, intraocular inflammation, retinal and/or choroidal circulation compromise, or hospitalizations in patients who receive Zimura. Because we currently have only one product candidate in clinical development, it is possible that a safety issue in any of our ongoing clinical trials for Zimura could impact all of our then-ongoing clinical trials.

As HtrA1 inhibition is a novel treatment approach for treating ocular disease, this treatment modality may present potentially unknown safety risks when tested in clinical trials that could not have been anticipated based on preclinical toxicology studies. In addition, if we are successful in formulating an HtrA1 product candidate, we intend to administer the product candidate by intravitreal injection, which poses the same safety risks outlined above with respect to intravitreal injections of Zimura.

In addition, there are several known safety risks specific to gene therapy, including inflammation resulting from a patient's immune response to the administration of viral vectors and the potential for toxicity as a result of chronic exposure to the expressed protein. Mediating a host body's immune response to introduced viral vectors has been and remains a challenge for gene therapies. For AAV gene therapy, "vector shedding" or the dissemination of AAV vectors away from the target tissue to other parts of the body, which can trigger a more serious and extensive immune response, is a known safety issue. Although subretinal injection, which is the method often used to administer ocular gene therapies, helps to control vector shedding beyond the eye, subretinal injection is a surgical procedure that requires significant skill and training for the administering surgeon and involves its own risks separate from the gene therapy vectors, including the risk of retinal detachment. In order to avoid accelerating damage to a subject's retina, subretinal injection for RHO-adRP patients in particular must be conducted under extremely low light levels using infrared technology, further complicating the surgical procedure. The margin for error with subretinal injections is extremely low and there are a limited number of retinal surgeons with experience in performing subretinal injections in the eye. In the event that we progress into clinical development with our RHO-adRP gene therapy product candidate, the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling studies, or any other gene therapy product candidate we may in-license or acquire, we may experience delays or other challenges for our development programs as a result of safety issues. For example, in order to generate useful clinical data for any of those gene therapy clinical trials, a retinal surgeon must repeat the same subretinal injection process multiple times and with consistency.

In addition to the currently known safety risks, there may be unknown risks to human health from gene therapies. Because gene therapy involves the introduction of concentrated quantities of AAV, as well as the introduction of persistent foreign genetic material into the human body, any safety risks may not manifest until much later, if at all. Gene therapies have only recently been used in the treatment of human diseases and the scientific and medical understandings of safety or other risks to humans continue to evolve. If gene therapies prove to be unsafe for humans, we likely will need to curtail or eliminate our gene therapy development programs or gene therapy products in development or commercialization, if any.

We do not have any internal manufacturing capabilities and use third parties to manufacture our product candidates on a contract or purchase order basis. Manufacturing issues, including technical or quality issues or issues with scaling up and building our capabilities for later-stage clinical manufacturing or for commercial manufacturing, may arise that could cause delays in our development programs or increase costs. We may experience delays in regulatory approval of our product candidates if we or our contract manufacturers do not satisfy applicable manufacturing regulatory requirements.

We do not have internal manufacturing facilities and use or plan to use outside contract manufacturers to manufacture Zimura, our HtrA1 inhibitors, our RHO-adRP gene therapy product candidate, the BEST1 gene therapy product candidates for which we have an option from Penn and UFRF, and any other product candidates that we may acquire or in-license. We have a limited number of personnel hired to supervise these outside vendors. Manufacturing for these product candidates could be complicated or present novel technical challenges. Problems with the manufacturing process, even minor deviations from the

established process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, in order to manufacture and supply any of our product candidates for later-stage clinical trials or on a commercial scale in the future, we will need to increase our manufacturing personnel and bolster our quality control and quality assurance capabilities. We may encounter problems hiring and retaining scientific and manufacturing personnel needed to oversee our manufacturing process, which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements. As we or any manufacturer we engage scales up manufacturing of any product candidate, we may encounter unexpected issues relating to the manufacturing processes or the quality, purity or stability of the product, and we may be required to refine or alter our manufacturing processes to address these issues. Resolving these issues could result in significant delays and may result in significantly increased costs. If we underestimate the demand for an approved product, given the long lead times required to manufacture or obtain regulatory approvals for our products, we could potentially face commercial drug product supply shortages. If we experience significant delays or other obstacles in producing any approved product at commercial scale, our ability to market and sell any approved products may be adversely affected and our business could suffer.

The manufacturing processes and the facilities of our third-party manufacturers are subject to inspection and approval by the FDA, referred to as a pre-approval inspection, before we can commence the commercial sale of any approved product candidate, and thereafter on an ongoing basis. Our third-party drug substance manufacturer for Zimura has undergone only two pre-approval inspections by the FDA, and has not yet gone through a pre-approval inspection for Zimura. Failure by our third-party manufacturers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidates may result in delays in the approval of our applications for marketing approval, as well as regulatory actions such as the issuance of FDA Form 483 notices of observations, warning letters or injunctions or the loss of operating licenses. If any of our third-party manufacturers are found to have delayed, denied, limited or refused a drug inspection, our drug substance or drug product could be deemed adulterated. Based on the severity of the regulatory action, our clinical or commercial supply of drug substance or drug product could be interrupted or limited, which could have a material adverse effect on our business.

Any problems in our manufacturing process or our third-party contract manufacturers' facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs. Problems in our manufacturing process or facilities also could restrict our ability to meet market demand for our products.

For a further discussion of the risks associated with our reliance on third-party manufacturers, see the risk factor herein entitled, "*We contract with third parties for the manufacture of and for providing starting materials for our product candidates for preclinical development activities and clinical trials and expect to continue to do so in the future. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products, which could delay, prevent or impair our development or commercialization efforts.*"

Our experience manufacturing Zimura is limited. We and our third-party contract manufacturers have not scaled up or validated the manufacturing process for Zimura for later-stage clinical or commercial manufacturing. We are only in the early stages of establishing manufacturing capabilities for our HtrA1 inhibitor program.

We currently use a single third-party manufacturer, Agilent Technologies, to supply us with the chemically synthesized drug substance for Zimura and a different, single third-party manufacturer, Ajinomoto Bio-Pharma Services, to provide fill/finish services for Zimura. In order to obtain and maintain regulatory approval for Zimura, our third-party manufacturers will be required to consistently produce the drug substance used in Zimura in commercial quantities and of specified quality and to execute fill/finish services on a repeated basis and document their ability to do so. If the third-party manufacturers are unable to satisfy this requirement, our business would be materially and adversely affected. To date, we have not yet scaled up the manufacturing process for Zimura beyond the scale used for developmental clinical batches, nor have we validated the manufacturing process.

Some of the standards of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, which establishes basic guidelines and standards for drug development in the United States, the European Union, Japan and other countries, do not apply to oligonucleotides, including aptamers. As a result, there are no established generally accepted manufacturing or quality standards for the production of Zimura. The lack of uniform manufacturing and quality standards among regulatory agencies may delay regulatory approval of Zimura.

For our HtrA1 inhibitor program, we seeking to engage contract manufacturers for producing the active pharmaceutical ingredient, or API, for our HtrA1 inhibitors. The time and efforts required for us to fully establish manufacturing capabilities for our HtrA1 inhibitor program may delay or impair our ability to develop this program in accordance with our expected timelines.

The manufacture of gene therapy products is complex with a number of scientific and technical risks, some of which are common to the manufacture of drugs and biologics and others are unique to the manufacture of gene therapies. We have limited experience with gene therapy manufacturing and are dependent on our third-party contract manufacturers and sole source suppliers.

Gene therapy drug products are complex and difficult to manufacture. We believe that the high demand for clinical gene therapy material and a scarcity of potential contract manufacturers may cause long lead times for establishing manufacturing capabilities for gene therapy drug development activities. Even after a manufacturer is engaged, because of the high demand for clinical gene therapy material and the limited availability of suitable manufacturing slots at most gene therapy manufacturers, there may be long lead times for scheduling a manufacturing run for our gene therapy product candidates, and any problems that arise during our manufacturing process may result in a longer delay to our timelines than we would otherwise expect. There may also be long lead times to manufacturing starting materials such as plasmids and cell lines, including high-quality starting materials that are cGMP compliant. In particular, plasmids, raw materials and other starting materials for gene therapy manufacture are usually sole sourced and a limited number of qualified suppliers are available. We are highly dependent on those suppliers providing us or our contract manufacturers with the necessary starting materials in a timely manner and with materials that meet our requirements. A failure to procure or a shortage of necessary starting materials likely would delay our manufacturing and development timelines.

A number of factors common to the manufacturing of biologics and drugs could also cause production issues or interruptions for gene therapies, including raw or starting material variability in terms of quality, cell line viability, productivity or stability issues, shortages of any kind, shipping, distribution and supply chain failures, growth media contamination, equipment malfunctions, facility contamination, labor problems, natural disasters, disruption in utility services, terrorist activities, or acts of god that are beyond our or our manufacturer's control. It is often the case that early stage research is conducted with materials that are not manufactured using cGMP starting materials, techniques or processes and which are not subject to the same level of analysis that would be required for clinical grade material. We may encounter difficulties in translating the manufacturing processes used to produce research grade materials to cGMP compliant processes, and any changes in the manufacturing process may affect the safety and efficacy profile of our product candidates. In addition, because early stage, pilot manufacturing is often done on a small scale, we may face challenges scaling up any early stage manufacturing to the scale necessary to support supply for clinical trials. In order to progress the development of our RHO-adRP gene therapy product candidate, the BEST1 product candidate for which we are planning to commence IND-enabling studies or any other gene therapy product candidate we may in-license or acquire, we will need to devote significant time and financial resources to establishing manufacturing processes that are sufficient for IND-enabling preclinical toxicology studies as well as clinical supplies. If we are not able to establish gene therapy manufacturing or related processes in a manner required for further development of our gene therapy product candidates, our development plans may be delayed or stalled and our business may be materially harmed.

We have engaged a gene therapy CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of our RHO-adRP drug product candidate. We have recently engaged a CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling studies.

We face substantial competition, which may result in others developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our product candidates from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies, as well as generic and biosimilar companies, worldwide. There are a number of pharmaceutical and biotechnology companies that are currently developing product candidates for the treatment of GA, Stargardt disease, RHO-adRP and LCA10, and there is at least one biotechnology company that is currently developing a product candidate for the treatment of Best disease. 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. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. We also will face similar competition with respect to any products or product candidates that we may seek to develop or

commercialize in the future. In particular, many companies are pursuing gene therapy approaches for orphan and age-related retinal diseases.

Our commercial opportunity could be reduced or eliminated if one or more of our competitors develop and commercialize products that are more effective, safer, have fewer or less severe side effects, are more convenient to use or are less expensive than our product candidates. The method of administration of Zimura, intravitreal injection, is commonly used to administer ophthalmic drugs for the treatment of severe disease and is generally accepted by patients facing the prospect of severe visual loss or blindness. A therapy that offers a less invasive method of administration, however, might have a competitive advantage over one administered by intravitreal injection, depending on the relative safety of the other method of administration.

Our competitors also may obtain FDA 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 relevant market. Furthermore, our ability to compete may be affected in many cases by insurers or other third-party payors, particularly Medicare, seeking to encourage the use of less expensive or more convenient products.

In the case of orphan diseases such as Stargardt disease, RHO-adRP or Best disease, should we be successful in development, our commercialization efforts may rely on non-patent market exclusivity periods under the Orphan Drug Act and the Hatch-Waxman Act. The Orphan Drug Act only provides exclusivity periods for the specific drug granted orphan drug designation for a specific indication. In addition, there are limited circumstances under each of the Orphan Drug Act and the Hatch-Waxman Act that could result in our loss of data and marketing exclusivity, which could allow a competitor to enter the market. Failure to maintain either data or market exclusivity period would have a material adverse effect on our ability to commercialize our product candidates.

Many of our competitors have significantly greater financial and human resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient enrollment for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our clinical development programs.

Based on publicly available information, we are aware of the following research and development programs that may be competitive with programs we are pursuing. Other competitive programs may exist of which we are not aware.

Competitive considerations for Dry AMD and GA:

- There are a number of products in preclinical research and clinical development by third parties to treat dry AMD, including several that are in development for GA secondary to dry AMD. In general, these product candidates can be categorized based on their proposed mechanisms of action. The mechanisms of action for these product candidates include inflammation suppression, such as complement system inhibitors and corticosteroids, visual cycle modulators, antioxidants and neuroprotectants, cell and gene therapies and vascular perfusion enhancers. We are aware that Apellis Pharmaceuticals, Inc., Roche AG, Novartis AG and MorphoSys AG, Hemera Biosciences, Inc., Gyroscope Therapeutics, Achillion Pharmaceuticals, Inc., and Catalyst Biosciences, Inc. each have complement inhibitors in development for dry AMD. We believe that the most advanced of these programs is Apellis's pegylated, synthetic peptide targeting complement protein C3. Following positive Phase 2 results for its C3 complement inhibitor product candidate, Apellis announced in September 2018 that it had dosed the first patient in a Phase 3 program for this product candidate. If Apellis's Phase 3 program for its C3 complement inhibitor product candidate is successful, it is likely that Apellis may obtain marketing approval for its product candidate in advance of when we could reasonably expect marketing approval for Zimura in GA or a product candidate from our HtrA1 inhibitor program in GA, if at all. Moreover, we are aware that several other companies have announced development programs for the treatment of dry AMD or GA targeting different mechanisms of action outside of the complement system.

Competitive considerations for Stargardt disease:

- There are a number of products in preclinical research and clinical development by third parties to treat Stargardt disease. We are aware that Sanofi, Acucela Inc., Alkeus Pharmaceuticals, Inc., Vision Medicines, Inc., Lin BioScience, Inc., Nightstar Therapeutics plc, ProQR Therapeutics N.V., Spark Therapeutics and Generation Bio Co. each have research or development programs in Stargardt disease. Four of these programs, Acucela, Alkeus, Vision Medicines and Lin BioScience, are exploring the use of oral therapeutics, while Sanofi, with technology provided by Oxford

BioMedica plc, Nightstar and Spark are each using a gene therapy approach and ProQR is using an RNA based approach. Acucela's product candidate is in Phase 3 development while Alkeus's and Sanofi's product candidates are each in Phase 2 development. Spark's program is in the research phase. In addition, several academic organizations have early stage programs in Stargardt disease.

Competitive considerations for RHO-adRP:

- There are a number of products in preclinical research by third parties to treat RHO-adRP. We are aware that multiple academic institutions have early stage gene therapy development programs in RHO-adRP. In addition, Nightstar Therapeutics plc has a preclinical AAV gene therapy program in RHO-adRP and ProQR Therapeutics N.V. is developing an early stage RNA-based therapeutic for RHO-adRP.

Competitive considerations for Best disease:

- We are aware that Nightstar Therapeutics plc has a preclinical AAV gene therapy program in Best disease.

Competitive considerations for LCA10:

- We are aware that Editas Medicine has a CRISPR gene editing program for LCA10, an IND for which was submitted in late 2018, ProQR Therapeutics N.V. is developing an RNA-based therapeutic for LCA10 that is currently in clinical development, and Generation Bio Co. has a preclinical program that utilizes ceDNA technology to target LCA10. In addition, several academic institutions have preclinical programs in LCA10.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing any of our product candidates that we develop if and when any such product candidate is approved.

As a company, we have no experience in the sale, marketing or distribution of pharmaceutical products. We currently do not have any sales, marketing or distribution infrastructure. To achieve commercial success for any approved product, we must either develop a sales, marketing and distribution organization or outsource those functions to third parties. We expect that our commercial strategy for any of our product candidates, including whether to retain commercial rights and market and sell the product candidate ourselves or to utilize collaboration, distribution or other marketing arrangements with third parties, would be determined based on a variety of factors, including the size and nature of the patient population, the disease area, the particular indication for which the product candidate is approved, the territory in which the product candidate may be marketed and the commercial potential for such product candidate. We are developing Zimura for GA secondary to dry AMD, which is a condition affecting a relatively large number of individuals, as well as for STGD1, which is a condition affecting a much more limited number of individuals. Our gene therapy programs are currently being developed for orphan IRDs with a limited number of affected individuals. If any of our product candidates are approved, the size and nature of the affected patient population will be an important factor in our commercial strategy. In addition, our commercial strategy would vary depending on whether the disease is typically treated by general ophthalmology practitioners, specialists, such as retinal specialists, or sub-specialists, such as retinal specialists with particular expertise in IRDs.

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

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

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to adequate numbers of physicians who may prescribe our products;
- the lack of complementary products to be offered by our sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and

- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

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

Even if any of our product candidates receives marketing approval, such product candidate may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success and the market opportunity for any of our products and product candidates may be smaller than we estimate.

The degree of market acceptance of Zimura or any other product candidate that we are developing or we may develop, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments, including the existing standard of care;
- any restrictions in the label on the use of our products in combination with other medications;
- any restrictions in the label on the use of our products by a subgroup of patients;
- restrictions in the label imposing a waiting period in between intravitreal or subretinal injections;
- our and any commercialization partner's ability to offer our products at competitive prices;
- availability of governmental and third-party payor coverage and adequate reimbursement;
- increasing reimbursement pressures on treating physicians due to the formation of accountable care organizations and the shift away from traditional fee-for-service reimbursement models to reimbursement based on quality of care and patient outcomes;
- willingness of the target patient population to try new therapies and of physicians to prescribe these therapies, particularly in light of the existing available standard of care or to the extent our product candidates require invasive procedures for administration, such as subretinal surgery;
- prevalence and severity of any side effects or perceived safety concerns, especially for new therapeutic modalities such as gene therapy; and
- whether competing products or other alternatives are more convenient or easier to administer, including whether co-formulated alternatives, alternatives that can be co-administered in a single syringe or alternatives that offer a less invasive method of administration than intravitreal injection or subretinal injection come to market.

For each of our Zimura trials where patients will receive multiple intravitreal injections on the same day, we have provided for a delay in the second intravitreal injection to minimize the risk of an unacceptable increase in intraocular pressure as a result of the volume of the multiple injections. In addition, certain of the Zimura dosing regimens we are evaluating require injections more frequently than once per month. If Zimura receives marketing approval for a particular indication and the approved label requires a waiting period between injections administered on the same day or a dosing regimen that requires multiple office visits per month, the potential market opportunity for Zimura may be limited to the extent that physicians and patients find such a waiting period or dosing regimen unacceptable.

In addition, the potential market opportunity for any product candidate is difficult to estimate precisely. Our estimates of the potential market opportunity for our product candidates include several key assumptions based on our expectations of the safety and effectiveness of the relevant product candidate, our industry knowledge, industry publications, market response to anti-VEGF agents currently approved for treatment of wet AMD and to Spark Therapeutics's Luxturna®, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, no independent source has verified

such assumptions and any of these assumptions could prove to be inaccurate, and the actual market for such product candidates could be smaller than our estimates of our potential market opportunity.

With respect to our programs for orphan diseases, our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Even if we are able to commercialize any of the product candidates that we may develop, the product may become subject to unfavorable pricing regulations, pricing dynamics, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.

The regulations that govern marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Health care reform, including increasing scrutiny of drug prices, is an issue of intense political focus, particularly in the United States. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals or in ways that could alter the mechanism by which pharmaceutical prices are negotiated or otherwise determined. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control or negotiation even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our or any commercialization partner's commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval and are widely accepted and prescribed or used by physicians.

In addition, even in countries where pharmaceuticals are not subject to strict pricing regulations through a governmental review and approval process, we may nonetheless face an unfavorable pricing environment as a result of political pressure or market dynamics. Because there is only one FDA-approved gene replacement therapy product, which began commercial sales in 2018, the pricing environment for gene therapies is in the very early stages of its development. Gene therapies are generally intended to be one-time treatments or, at a minimum, to provide a benefit over an extended period lasting several years. If we are successful in obtaining marketing approval for any of our gene therapy product candidates, we will need to convince third-party payors of the value that our gene therapy product offers. Third-party payors may be unwilling to accept substantial upfront costs for a therapy where the benefits are realized over a period of years during which the patient may no longer be enrolled in the payor's plan. Furthermore, the pricing for products intended to treat orphan diseases in particular may be perceived as too high to be justified. The perceived high cost for pharmaceutical products to treat orphan diseases may attract increased political and public scrutiny. Moreover, if we obtain marketing approval for a product candidate, such as Zimura, in more than one indication, including, for example in an orphan indication such as STGD1 and a non-orphan indication such as GA secondary to dry AMD, such a product candidate likely would only be sold at one price in any given country, regardless of the indications for which it is prescribed. This dynamic may result in our charging a price that does not generate profits in each indication for which the product is approved.

Our ability and the ability of any commercialization partner to commercialize a product candidate successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A major trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors, particularly Medicare, have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications and encouraging the substitution of lower cost or generic products. Pricing pressures recently experienced by the pharmaceutical industry may be further exacerbated by legislative and policy changes under consideration by the Trump Administration and many states. For example, the Trump Administration has expressed an interest in authorizing and/or directing the Center for Medicare & Medicaid Service or other agencies of the U.S. government to negotiate prices for drugs covered by Medicare directly with pharmaceutical companies. If this were to occur, especially for AMD drugs where a large portion of the patient population is over the age of 65 and is therefore covered by Medicare, there could be significant downward pressure on prices charged, not only for patients covered by Medicare, but also for patients covered by private insurers who may follow the government's lead on price. Moreover, increasingly, third-party

payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize or any commercialization partner commercializes on our behalf, and, even if these are available, the level of reimbursement may not be satisfactory.

Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining 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. We or any commercialization partner may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies that may be on the market. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs, and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States, a policy that President Trump has expressed interest in pursuing. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our and any commercialization partner's inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

The pricing of prescription pharmaceuticals is subject to governmental control outside of the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or a commercialization partner may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Product liability lawsuits against us or any future commercialization partner could divert resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop or in-license.

We face an inherent risk of product liability exposure related to the testing of any product candidate that we develop in human clinical trials, and we and any future commercialization partner will face an even greater risk if we commercially sell any products that we develop or in-license. If we become subject to or otherwise cannot successfully defend ourselves against claims that our product candidates or our products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop or in-license;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced time and attention of our management to pursue our business strategy; and

- the inability to commercialize any products that we may develop or in-license.

We currently hold $10.0 million in product liability insurance coverage in the aggregate, with a per incident limit of $10.0 million, which may not be adequate to cover all liabilities that we may incur. We will need to increase our insurance coverage when and if we begin commercializing an approved product. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. In addition, if a commercialization or collaboration partner were to become subject to product liability claims or were unable to successfully defend themselves against such claims, any such commercialization or collaboration partners could be more likely to terminate such relationship with us and therefore substantially limit the commercial potential of our products.

Risks Related to Our Dependence on Third Parties

We contract with third parties for the manufacture of and for providing starting materials for our product candidates for preclinical development activities and clinical trials and expect to continue to do so in the future. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products, which could delay, prevent or impair our development or commercialization efforts.

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of any of our product candidates and have a limited number of personnel hired to supervise outside contract manufacturers. We currently rely upon and expect to continue to rely upon third-party contract manufacturers to manufacture preclinical and clinical supplies of product candidates we are developing or may develop and commercial supplies of products if and when approved for marketing by applicable regulatory authorities. Furthermore, we and our contract manufacturers currently rely upon and for the foreseeable future expect to continue to rely upon sole-source suppliers of certain raw materials, plasmids and other specialized components of production used in the manufacture and fill/finish of our product candidates.

We currently rely exclusively upon, and purchase on a purchase order basis, a single third-party manufacturer to provide Zimura drug substance and a different single third-party manufacturer to provide fill/finish services for Zimura. We do not currently have any contractual commitments for the supply of Zimura drug substance. We also do not currently have arrangements in place for redundant supply or a second source for drug substance for Zimura or a second source for fill/finish services for Zimura. We purchase the polyethylene glycol, or PEG, reagent used to modify the chemically synthesized aptamer in Zimura on a purchase order basis from a single third-party supplier. We do not currently have any contractual commitments for supply of the PEG reagent we use for Zimura. The prices for manufacturing activities that are not yet contractually committed may vary substantially over time and adversely affect our financial results.

For our HtrA1 inhibitor program, we are seeking to engage contract manufacturers for producing the API for our HtrA1 inhibitors. We have engaged a gene therapy CDMO for preclinical and Phase 1/2 clinical supply of our RHO-adRP product candidate. We have recently engaged a CDMO for preclinical and Phase 1/2 clinical supply of the BEST1 gene therapy drug product candidate for which we are planning to commence IND-enabling studies.

Our current and anticipated future dependence upon others for the manufacture of the product candidates that we are developing or may develop may adversely affect our business plan and future growth. For example, any performance failure or differing priorities on the part of our existing or future manufacturers could delay preclinical or clinical development or marketing approval of our product candidates. Our dependence on third party manufacturers may limit our ability to commercialize on a timely and competitive basis any products that receive marketing approval.

If any of our third-party manufacturers, fill/finish providers or sole-source suppliers fail to fulfill our purchase orders, or if any of these manufacturers or suppliers should become unavailable to us for any reason, including as a result of capacity constraints, differing priorities, regulatory compliance issues, financial difficulties or insolvency, we believe that there are a limited number of potential replacement manufacturers or sole source suppliers, and we likely would incur added costs and delays in identifying or qualifying such replacements. We may be unable to establish agreements with such replacement manufacturers, fill/finish providers or sole-source suppliers or to do so on acceptable terms.

In addition, to the extent that we or our third party manufacturers rely on materials that are sourced outside the United States, our supplier relationships could be interrupted due to international supply disruptions, including those caused by geopolitical and other issues. For example, trade disputes, trade negotiations or the imposition of tariffs between the United States and its trading partners could cause delays or disruptions in our supply of starting materials for our product candidates.

Reliance on third-party manufacturers entails additional risks, including:

- our product candidates may compete with other product candidates and products for access to a limited number of suitable manufacturing facilities that operate under cGMP conditions;
- reliance on the third party for regulatory compliance, quality assurance and quality control;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products and harm our business and results of operations.

We rely upon third parties in conducting our preclinical development activities and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We have in the past and expect in the future to rely upon third parties, such as contract research organizations, or CROs, clinical data management organizations, biostatisticians, academic research collaborators, medical institutions (including reading centers) and clinical investigators, in conducting our preclinical testing and clinical trials for our product candidates. We or these third parties may terminate their engagements with us at any time for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities could potentially be delayed and could potentially be very costly.

Our reliance on these third parties for preclinical testing and clinical development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we would not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and would not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors.

We also rely upon other third parties to store, package, label and distribute drug supplies for our clinical trials and to store materials and drug substance for our preclinical development activities. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We rely on third-party researchers to advance our sponsored research programs. These arrangements may not ultimately yield any promising product candidates for preclinical or clinical development. We may not be able to fully realize the benefits of any intellectual property generated by these arrangements.

Part of our strategy involves collaborative sponsored research to be performed by third-party research institutions. Although we seek to direct this research and advise on the design of these projects as well as critical development decisions, this research is being performed by individuals who are not our employees and the timeline and quality of the research efforts are outside of our direct control. Academic investigators and other researchers may have different priorities than we do as a biopharmaceutical drug development company. Confidential information and new inventions derived from these research efforts may be disclosed through publications or other means prior to our being able to protect such intellectual property through the filing of patent applications. Our third-party research partners may not be able to obtain or maintain full ownership of inventions that are derived from the research or associated rights, which may limit their ability to provide us with a license to all relevant intellectual property on terms and conditions that are acceptable to us. Even if our collaborative research efforts yield promising results or new technological advances, they may not ultimately result in our being able to protect, develop or exploit the resulting intellectual property.

If we are not able to establish collaborations to advance our development programs, we may have to alter our development and commercialization plans.

The development and potential commercialization of our product candidates is likely to require substantial additional cash to fund expenses. In addition, the commercialization of a product candidate in markets outside of the United States requires regulatory expertise and commercial capabilities that are specific to the local market. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

We may enter into collaborations with third parties for the development or commercialization of our product candidates. These collaborations carry numerous risks. If any of our collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We may utilize a variety of types of collaboration, distribution and other marketing arrangements with third parties to commercialize our product candidates, either in the United States, or in markets outside the United States. We also may seek third-party collaborators for development and commercialization of other product candidates we may develop. Our likely collaborators for any sales, marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. If we do enter into any additional arrangements with third parties in the future, we would likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our

ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates could pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations and may not perform their obligations as expected;
- collaborators may deemphasize or not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus, changes in product candidate priorities or available funding or changes in priorities as a result of a merger, acquisition or other corporate restructuring or transaction;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- we could grant exclusive rights to our collaborators, which would prevent us from collaborating with others;
- disagreements or disputes with collaborators, including disagreements or disputes over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of products or product candidates, might lead to additional responsibilities for us with respect to product candidates or might result in litigation or arbitration, any of which would divert management attention and resources, be time-consuming and be expensive;
- collaborators with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights, may infringe the intellectual property rights of third parties, may misappropriate our trade secrets or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator, our breach of the terms of the collaboration or other reasons and, if terminated, we may need to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If a collaborator of ours were to be involved in a business combination or other transaction, the foregoing risks would be heightened, and the business combination or transaction may divert attention or resources or create competing priorities. The collaborator may delay or terminate our product development or commercialization program. If one of our collaborators terminates its agreement with us, we could find it more difficult to attract new collaborators and the perception of our company in the business and financial communities could be adversely affected.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all.

We depend on licenses and sublicenses for development and commercialization rights to Zimura and our RHO-adRP gene therapy product candidate. These license arrangements, as well as the Inception 4 Merger Agreement, impose diligence obligations on us. We may enter into similar arrangements with respect to future product candidates, including any license agreement we enter into with Penn and UFRF for the BEST1 gene therapy product candidates for which we hold an option. Termination of licenses or the failure by us or our licensees, including our potential future commercialization or collaboration partners, to comply with obligations under these or other agreements could materially harm our business and prevent us from developing or commercializing our products and product candidates.

We are party to a license agreement with Archemix on which we depend for rights to Zimura and a separate license agreement with UFRF and Penn on which we depend for rights to our RHO-adRP gene therapy product candidate. These agreements generally impose diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. Generally, the diligence obligations contained in these agreements require us to use commercially reasonable efforts to develop, seek regulatory approval for and commercialize the applicable product candidate in the United States and certain territories outside of the United States, including the European Union, Japan and such other markets where it would be commercially reasonable to do so. Under the license agreements for our product candidates, we would not be able to avoid our payment obligations even if we believed a licensed patent right was invalid or unenforceable because the license agreements provide that our licenses to all licensed patent rights would terminate if we challenge the validity or enforceability of any licensed patent right. The Inception 4 Merger Agreement, pursuant to which we acquired our HtrA1 inhibitor program, also imposes a certain diligence obligation and certain milestone payment obligations on us. We may enter into acquisition or licensing agreements in the future that would impose similar obligations on us, particularly as we continue to pursue our strategy to potentially acquire or in-license additional products, product candidates or other technologies and expand our product pipeline.

We will need to enter into a definitive license agreement with Penn and UFRF for us to continue developing the Best1 gene therapy product candidate for which we are planning to commence IND-enabling studies and any other Best1 gene therapy product candidates from this program. We may not be successful in agreeing to a definitive license agreement with Penn and UFRF, and even if we execute a license agreement, the agreement may contain terms that may be unfavorable to us.

If we fail to comply with our obligations under current or future acquisition and licensing agreements, or otherwise breach an acquisition or licensing agreement as a result of our own actions or inaction or the actions or inactions of our commercialization or collaboration partners, our counterparties may have the right to terminate these agreements, in which event we might not have the rights or the financial resources to develop, manufacture or market any product that is covered by these agreements. Our counterparties also may have the right to convert an exclusive license to non-exclusive in the territory in which we fail to satisfy our diligence obligations, which could materially 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 restated agreements with less favorable terms, seek alternative sources of financing or cause us to lose our rights under these agreements, including our rights to Zimura, our RHO-adRP gene therapy product candidate and other important intellectual property or technology. Any of the foregoing could prevent us from commercializing our product candidates, which could have a material adverse effect on our operating results and overall financial condition. In the case of our limited diligence obligation under the Inception 4 Merger Agreement, a potential breach of our obligation to use commercially reasonable efforts to develop an HtrA1 inhibitor could lead to a lawsuit with the former equityholders of Inception 4 and result in potential liability to us of up to $5 million.

In addition to the above risks, certain of our intellectual property rights are sublicenses under intellectual property owned by third parties, in some cases through multiple tiers. The actions of our licensors may therefore affect our rights to use our sublicensed intellectual property, even if we are in compliance with all of the obligations under our license agreements. Should our licensors or any of their upstream licensors fail to comply with their obligations under the agreements pursuant to which they obtain the rights that are sublicensed to us, or should such agreements be terminated or amended, our ability to develop and commercialize Zimura and other product candidates may be materially harmed. While the applicable agreements may contain contractual provisions that would in many instances protect our rights as a sublicensee in these circumstances, these provisions may not be enforceable and may not protect our rights in all instances. Further, we do not have the right to control the prosecution, maintenance and enforcement of all of our licensed and sublicensed intellectual property, and even when we do have such rights, we may require the cooperation of our licensors and their upstream licensors, which may not be forthcoming. Our business could be materially adversely affected if we are unable to prosecute, maintain and enforce our licensed and sublicensed intellectual property effectively.

Moreover, the license agreement for our RHO-adRP gene therapy product candidate reserves for the licensing academic institutions the right to continue to practice for research purposes, the inventions covered by the intellectual property rights that we have in-licensed. These licensing institutions or their collaborators may generate scientific, preclinical or clinical data with respect to our product candidate, separate from our research and development efforts, that is inconsistent with other data for such product candidate, including additional preclinical and clinical data that we develop. Investigators at these institutions may publish, present, or otherwise publicly disclose this data, which may have an adverse impact on the prospects of the development of our product candidate and may harm our business. In addition, these institutions may use these data to support new patent applications which could result in the issuance of patents that may limit our freedom to operate without our obtaining additional licenses to these newly developed inventions.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain or do not maintain patent protection for our technology and products during the period of their commercialization, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be adversely affected.

The U.S. patent rights covering Zimura as a composition of matter are expected to expire in 2025. The U.S. patent rights covering methods of treating certain complement protein mediated disorders with Zimura are expected to expire in 2026. The European patent rights covering the composition of matter of Zimura and methods of treating certain complement protein mediated disorders with Zimura are expected to expire in 2025. As we expect the clinical development of Zimura to continue for at least the next several years, these expiration dates may be prior to the date by which we would be able to commercialize Zimura in the United States or Europe if we seek and obtain marketing approval. Once our patents expire, we may not be able to exclude competitors from commercializing products similar or identical to ours. Even if we are able to obtain marketing approval for and commercially launch Zimura prior to the expiration of these patents, the remaining term of those patents may be shorter than we anticipate. Although our existing patent rights for our HtrA1 inhibitors and our RHO-adRP gene therapy product candidate are not expected to expire until 2037 or 2039, we face the same risk with those product candidates and any future product candidates that we may develop.

Depending on potential delays in the regulatory review process for Zimura, we may be able to obtain patent term extension for one of our patents in the United States under the Hatch-Waxman Act, which permits a patent extension term of up to five years as partial compensation for patent term effectively lost during product development and the FDA regulatory review process occurring after the issuance of a patent, but we can provide no assurances that such an extension term will be obtained. Similar to the patent term extension available in the United States, the regulatory framework in the European Union and certain other foreign jurisdictions provides the opportunity to extend the term of a patent that covers an approved drug in certain circumstances. Notwithstanding the availability of patent term extension provisions, we may not be granted patent term extensions because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements, such as using diligent efforts to develop a drug candidate. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term or scope of any such extension is less than we request, any period during which we have the right to exclusively market our product would be shorter than we would otherwise expect, and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

Certain of our licensed patent rights for Zimura are method-of-treatment patents. Method-of-treatment patents are more difficult to enforce than composition-of-matter patents because of the risk of off-label sale or use of a drug for the patented method. The FDA does not prohibit physicians from prescribing an approved product for uses that are not described in the product's labeling. Although use of a product directed by off-label prescriptions may infringe our method-of-treatment patents, the practice is common across medical specialties, particularly in the United States, and such infringement is difficult to detect, prevent or prosecute. Off-label sales of other products having the same drug substance as Zimura or any other product candidates we may develop would limit our ability to generate revenue from the sale of Zimura or such other product candidates, if approved for commercial sale. In addition, European patent law generally makes the issuance and enforcement of patents that cover methods of treatment of the human body difficult. Further, once the composition-of-matter patents relating to Zimura or any other product candidate in a particular jurisdiction, if any, expire, competitors will be able to make, offer and sell products containing the same drug substance as Zimura or such other product candidate in that jurisdiction so long as these competitors do not infringe any of our other patents covering Zimura's composition of matter or method of use or manufacture, do not violate the terms of any marketing or data exclusivity that may be granted to us by regulatory authorities and obtain any necessary marketing approvals from applicable regulatory authorities. In such circumstances, we also may not be able to detect, prevent or prosecute off-label use of such competitors' products containing the same drug substance as Zimura, even if such use infringes any of our method-of-treatment patents.

The BEST1 gene therapy product candidate for which we are planning to commence IND-enabling activities is not currently covered by a patent or pending patent application. In developing and advancing this product candidate, we may seek to rely on the prospect of generating new intellectual property during development of the product candidate or the potential for non-patent market exclusivity, including regulatory exclusivity as a result of the Orphan Drug Act. If we, together with Penn and UFRF, are unable to generate data to support a patent or patent application to cover this product candidate or if we are unable to obtain non-patent market exclusivity, we may not be able to exclude competitors from marketing an identical or substantially similar product.

For our sponsored research agreements with UMMS and Penn, we are generally relying on our university collaborators to generate research and data to support new patent applications. The results of any sponsored research are uncertain and the interests of the universities and university researchers are not necessarily aligned with our interests as a commercial entity. The research may generate limited patentable results or data, or none at all. Furthermore, the universities generally control the filing, prosecution and maintenance of any patents or patent applications resulting from the sponsored research. Therefore, we may not be able to obtain any patent or other exclusivity protections as a result of our collaborative gene therapy sponsored research programs, which could materially diminish or eliminate the value of these programs.

The Hatch-Waxman Act also permits the manufacture, use, offer for sale, sale or importation of a patented invention other than a new animal drug or veterinary biological product, if the manufacture, use, offer for sale, sale or importation is solely for uses that are reasonably related to development of information that could be submitted to the FDA. For this reason, our competitors might be able under certain circumstances to perform activities within the scope of the U.S. patents that we own or under which we are licensed without infringing such patents. This might enable our competitors to develop during the lifetime of these patents drugs that compete with our product candidates, if they are ultimately approved.

Our issued patents may not be sufficient to provide us with a competitive advantage. For example, competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. Even if our owned or licensed patent applications issue as patents, they may not issue with a scope broad enough to provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. We could also fail to take the required actions and pay the necessary governmental fees to maintain our patents.

The issuance of a patent is not conclusive as to its inventorship, ownership, scope, term, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. For example, if we receive marketing approval for our product candidates, other pharmaceutical companies may seek approval of generic versions of our products with the FDA or regulatory authorities in other jurisdictions. We may then be required to initiate proceedings against such companies in order to enforce our intellectual property rights. The risk of being involved in such proceedings is likely to increase if our products are commercially successful. In any such proceedings, the inventorship, ownership, scope, term, validity and enforceability of our patents may be challenged. These and other 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 prevent others from using or commercializing similar or identical technology and products or from launching generic versions of our products, or could limit the duration of the patent protection of our technology and products. The launch of a generic version of one of our products in particular would be likely to result in an immediate and substantial reduction in the demand for our product, which could have a material adverse effect on our business. 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 patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

The patent prosecution process is expensive and time-consuming, is highly uncertain and involves complex legal and factual questions. Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing in the United States and in certain foreign jurisdictions patent applications related to our novel technologies and product candidates that are important to our business.

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. 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. In addition, we may not pursue or obtain patent protection in all major markets. Moreover, in some circumstances, we do not have the right to control the preparation, filing or prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties or covering technology that a collaboration or commercialization partner may develop, the eventual commercialization of which could potentially entitle us to royalty payments. In some circumstances, our licensors have the right to enforce the licensed patents without our involvement or consent, or to decide not to enforce or to allow us to enforce the licensed patents. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. If any such licensors fail to maintain such patents, or lose rights to those patents, the rights that we have licensed may be reduced or eliminated and our ability to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign jurisdictions 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. 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 be certain that we or our licensors were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions. Moreover, the U.S. Patent and Trademark Office, or USPTO, might require that the term of a patent issuing from a pending patent application be disclaimed and limited to the term of another patent that is commonly owned or names a common inventor. As a result, the issuance, scope, validity, term, enforceability and commercial value of our patent rights are highly uncertain.

Our pending and future patent applications, and any collaboration or commercialization partner's pending and future patent applications, may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. In particular, during prosecution of any patent application, the issuance of any patents based on the application may depend upon our or their ability to generate additional preclinical or clinical data that support the patentability of our proposed claims. We or any collaboration or commercialization partner may not be able to generate sufficient additional data on a timely basis, or at all. Moreover, changes in either the patent laws or interpretation of the patent laws in the United States or other countries may diminish the value of our or a collaboration or commercialization partner's patents or narrow the scope of our or their patent protection.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. The Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law in September 2011, and many of the substantive changes became effective in March 2013. The Leahy-Smith Act revised United States patent law in part by changing the standard for patent approval from a "first to invent" standard to a "first to file" standard and developing a post-grant review system. This legislation changed United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 2013. For example, if we are the first to invent a new product or its use, but another party is the first to file a patent application on this invention, under the new law the other party may be entitled to the patent rights on the invention. Furthermore, the Leathy-Smith Act expanded the ability of third parties to challenge the patents held by patentees through administrative reviews at the USPTO, which may facilitate others to challenge our patents.

Moreover, we may be subject to a third-party preissuance submission of prior art to the USPTO, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review, interference proceedings or other patent office proceedings or litigation, in the United States or elsewhere, challenging our patent rights or the patent rights of others. Based on available information, we believe that *inter partes* review proceedings, brought by financial investors who may be selling short the stock of the patent holder, are becoming more prevalent. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our 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. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

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

Competitors may infringe or otherwise violate our patents, trademarks, copyrights or other intellectual property. To counter infringement or other violations, we may be required to file claims, which can be expensive and time consuming. Any such claims could provoke these parties to assert counterclaims against us, including claims alleging that we infringe their patents or other intellectual property rights. In addition, in a patent infringement proceeding, a court may decide that one or more of the patents we assert is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to prevent the other party from using the technology at issue on the grounds that our patents do not cover the technology. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In such a case, we could ultimately be forced to cease use of such marks. In any intellectual property litigation, even if we are successful, any award of monetary damages or other remedy we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Third parties may initiate legal proceedings or take other actions alleging that we are infringing or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of any future collaboration and commercialization partners to develop, manufacture, market and sell our product candidates and products and use our proprietary technologies without infringing or otherwise violating the intellectual property and other proprietary rights of third parties. New patent applications in the field of biotechnology and pharmaceuticals, and gene therapies in particular, are being filed at a rapid pace.

There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We or any future collaboration and commercialization partners may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference, derivation, re-examination, post-grant review, *inter partes* review, opposition, cancellation or similar proceedings before the USPTO or its foreign counterparts. The risks of being involved in such litigation and proceedings may also increase as our or their product candidates near commercialization.

Third parties may assert infringement claims against us or our collaboration or commercialization partners based on existing or future intellectual property rights. We or they may not be aware of all such intellectual property rights potentially relating to our product candidates and their manufacture and uses. There is a lag between the filing of a patent application, which generally establishes the priority date of a patent claim, and the publication of such patent application. During the period between filing of a patent application and publication of the application, we would not otherwise have a means of discovering the existence or extent of the claimed inventions contained in a filed but unpublished patent application. Patent applications are often drafted broadly, and the scope of patent claims that may ultimately issue may not be known until several years after a patent application is filed and published. We may make development or pipeline decisions based on our belief that our product candidates can be distinguished from patent claims contained in published patent applications or issued patents, that patent claims contained in published patent applications are unlikely to issue as drafted, or that claims contained in issued patents are invalid. These positions regarding third-party intellectual property may not ultimately be successful in litigation. Thus, we do not know with certainty that our product candidates, or our intended commercialization thereof, does not and will not infringe or otherwise violate any third party's intellectual property.

If we are or any of our future collaboration or commercialization partners is found to infringe or otherwise violate a third party's intellectual property rights, we or they could be required to obtain a license from such third party to continue developing and marketing our or their products and technology or to continue using a trademark. However, we or our future collaboration and commercialization partners may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or they were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us or our collaboration and commercialization partners and could require us or them to make substantial licensing and royalty payments. We or our future collaboration and commercialization partners could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us or our future collaboration and commercialization partners from commercializing our or their product candidates or force us or them to cease some of our business operations, which could materially harm our business. Claims that we or our future collaboration and commercialization partners have misappropriated the confidential information or trade secrets of third parties could expose us or them to similar liabilities and have a similar negative impact on our business.

We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees and contractors were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees and contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees or contractors have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's or contractor's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact conceives or develops intellectual property that we regard as our own. Moreover, because we acquired rights to our product candidates from third parties, we must rely upon these third parties

and their successors' practices, and those of their predecessors, with regard to the assignment of intellectual property therein, including the intellectual property rights protecting the HtrA1 inhibitors we acquired in the Inception 4 acquisition transaction. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel.

Intellectual property litigation could cause us to spend substantial resources and could distract our personnel from their normal responsibilities.

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, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by governmental patent offices, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and patent offices in foreign countries in several stages over the lifetime of the patent. The USPTO and patent offices in foreign countries require compliance with a number of procedural, documentary, fee payment and other requirements during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of a patent or patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and products, we also rely upon trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have executed such agreements with each party that may have or have had access to our trade secrets. Moreover, because we acquired certain rights to Zimura from Archemix, we must rely upon Archemix's and its successors' practices, and those of its predecessors, with regard to the protection of Zimura-related trade secrets before we acquired it. Similarly, because we acquired our HtrA1 inhibitor program through the acquisition of Inception 4, we are relying upon Inception 4's practices with regard to the protection of trade secrets and intellectual property rights for the period prior to our acquisition of Inception 4. Any party with whom we or they have executed a non-disclosure and confidentiality agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Our proprietary information may also be obtained by third parties by other means, such as breaches of our physical or computer security systems.

Detecting the disclosure or misappropriation of a trade secret and enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom

they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

Risks Related to Information Technology

We rely significantly upon information technology systems and any failure, inadequacy, interruption or security lapse of these systems could harm our ability to operate our business effectively.

In the ordinary course of our business, we and our third-party contractors maintain personal and other sensitive data on our and their respective networks, including our intellectual property and proprietary or confidential business information relating to our business and that of our clinical trial participants, business partners and employees. In particular, we rely on contract research organizations and other third parties to store and manage information from our clinical trials. The secure maintenance of this sensitive information is critical to our business and reputation.

We have implemented a number of measures to protect our information technology systems. These measures include, among others, creation of a cyber-security governance team and standard operating procedures for responding to any cyber-security breaches, mandatory cyber-security training for our employees and consultants with access to our information technology systems and engagement of a third-party vendor to assess our informational technology systems and potential vulnerabilities.

Despite the implementation of security measures, our internal computer systems and those of our third-party contractors are vulnerable to compromise, damage, loss or exfiltration from cyber-attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. In particular, companies and other entities and individuals have been increasingly subject to a wide variety of security incidents, cyber-attacks, phishing scams and other attempts to gain unauthorized access to systems and information, including through social engineering. The number and complexity of these threats continue to increase over time. These threats can come from a variety of sources, ranging in sophistication from individual hackers to state-sponsored attacks. Cyber threats may be broadly targeted, or they may be custom-crafted against our information systems or those of our third-party contractors.

For information stored with our third-party contractors, we rely upon, and the integrity and confidentiality of such information is dependent upon, the risk mitigation efforts such third-party contractors have in place. In the recent past, cyber-attacks have become more prevalent and much harder to detect and defend against. Our and our third-party contractors' respective network and storage applications may be subject to unauthorized access by hackers or breached due to operator error, malfeasance or other system disruptions. We might not anticipate or immediately detect such incidents and the damage caused by such incidents. System failures, data breaches and any unauthorized access or disclosure of our information or intellectual property could compromise our intellectual property and expose sensitive business information. System failures or accidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our research and development activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. Moreover, if a breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed and our reputation and credibility could be damaged.

A data security breach could also lead to public or unauthorized exposure of personal information of our clinical trial patients, our employees or others. Cyber-attacks and the measures we implement to prevent, detect, and respond to them could cause us to incur significant remediation costs, result in product development delays, disrupt key business operations, expose us to contractual damages and/or regulatory liability, require us to make certain breach notifications, divert the attention of our management and key information technology resources, harm our reputation and deter patients, clinical investigators or other business partners from participating in our clinical trials or otherwise working with us. Any loss of preclinical data or clinical trial data 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 public disclosure of confidential or proprietary information, we could incur liability and our product research, development and commercialization efforts could be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could have a material adverse effect on our business, financial condition or results of operations.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example,

the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements has required and will continue to require significant time, resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the European Union. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices, and any non-compliance by us or our employees, consultants or contractors could lead to government enforcement actions, private litigation, significant fines and penalties, or reputational harm and could have a material adverse effect on our business, financial condition or results of operations.

Risks Related to Regulatory Approval and Marketing of our Product Candidates and Other Legal Compliance Matters

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and by the EMA and comparable regulatory agencies in other countries.

In general, the FDA and similar regulatory authorities outside the United States require two adequate and well-controlled clinical trials demonstrating safety and effectiveness for marketing approval for an ophthalmic pharmaceutical product. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely upon third-party CROs to assist us in this process. Securing marketing approval requires obtaining positive safety and efficacy data from required clinical trials, as well as the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing processes to, and inspection of manufacturing facilities by, the relevant regulatory authorities. The FDA or other regulatory authorities may determine that a product candidate that we may develop is not effective, is only moderately effective or has undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use.

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

Marketing approval of novel product candidates such as Zimura or our RHO-adRP gene therapy product candidate manufactured using novel manufacturing processes can be more expensive and take longer than for other, more well-known or extensively studied pharmaceutical or biopharmaceutical products, due to regulatory agencies' lack of experience with them. We believe that the FDA has only granted marketing approval for one aptamer product and one gene replacement product to date. This lack of experience may lengthen the regulatory review process, require us to conduct additional studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions.

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

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed in such jurisdictions.

In order to market and sell our product candidates in the European Union and many other jurisdictions, we or our third-party commercialization partners must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional preclinical or clinical testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our third-party commercialization partners may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We and our third-party commercialization partners may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

It remains to be seen how, if at all, Brexit will actually occur and how, if at all, Brexit will impact regulatory requirements for the approval of pharmaceutical product candidates and the sale of pharmaceutical products in the United Kingdom and the European Union.

We currently do not have orphan drug designations or orphan drug exclusivity for any product. If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, 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 5 in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

If we request orphan drug designation for any of our product candidates in one or more indications, there can be no assurances that the FDA or the European Commission will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for a product that constitutes the same drug

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

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In particular, the concept of what constitutes the "same drug" for purposes of orphan drug exclusivity is unclear in the context of gene therapies, and the FDA has issued draft guidance suggesting minor variations in the construct of a gene therapy that lead to improvements in safety or efficacy may result in the determination that a drug is a "different drug". In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

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

A fast track designation or grant of priority review status by the FDA may not actually lead to a faster development or regulatory review or approval process. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

The FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and if the product demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

The FDA has broad discretion whether or not to grant fast track designation or priority review status, so even if we believe a particular product candidate is eligible for such designation or status the FDA could decide not to grant it. Even though a product has received fast track designation and may be eligible for priority review status, a sponsor may not ultimately experience a faster development process, review or approval compared to conventional FDA procedures.

A breakthrough therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates would receive marketing approval.

In 2012, Congress enacted the Food and Product Administration Safety and Innovation Act, or FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as "breakthrough therapies." A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to

breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the products no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we or our third-party commercialization partners may be subject to penalties if we or our third-party commercialization partners or our or their manufacturers fail to comply with regulatory requirements or if we or our third-party commercialization partners or our or their manufacturers experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we or our commercialization partners obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control and quality assurance, complaints and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or may be subject to significant conditions of approval or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy.

The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions 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, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on distribution or use of a product;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- damage to relationships with any potential collaborators;

- unfavorable press coverage and damage to our reputation;
- 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;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our products.

Non-compliance with European Union requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the European Union's requirements regarding the protection of personal information, such as the GDPR, can also lead to significant penalties and sanctions.

Our and our potential commercialization partners' relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us and our commercialization partners to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors may expose us and our commercialization partners to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we and our commercialization partners market, sell and distribute any products for which we or they obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals, with data collection beginning in August 2013; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our financial results. We are developing and implementing a corporate compliance program designed to ensure that we will market and sell any future products that we successfully develop from our product candidates in compliance with all applicable laws and regulations, but we cannot guarantee that this program will protect us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our or our commercialization partners' operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us or them, we or they may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our or their operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Our operations may be dependent on the normal function on the FDA, the SEC and other government agencies. The inability of those agencies to obtain necessary funding and other effects from the political process could prevent those agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government funding levels, ability to hire and retain key personnel and to accept the payment of user fees, and statutory, regulatory, and policy changes. Government funding of the FDA, the SEC and other government agencies on which our operations may rely is subject to the political process, which is inherently fluid and unpredictable. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, in our operations as a public company, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations. In addition, the Trump Administration has taken several executive actions, including the issuance of a number of executive orders, that could affect federal agencies, including the FDA. Those executive actions, some of which are still being implemented, may impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities, which could negatively impact our business.

Current and future legislation and regulations may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize our product candidates and affect the prices we, or they, may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell any products for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any future collaborators, may receive for any approved products.

In March 2010, President Barack H. Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA. Among the provisions of the ACA of potential importance to our business and our product candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription products and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report product samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2025 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

Since enactment of the ACA, there have been numerous legal challenges and congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." Congress may consider other legislation to replace or amend elements of the ACA during the current congressional session.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in

California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued the payments were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business are not yet known.

We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Trump Administration have stated that they will address such costs through new legislative and administrative measures. In May 2018, the Trump Administration announced a plan that would include several initiatives designed to lower drug prices and additional similar proposals from HHS and CMS have followed. At the state level, individual states are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing. Additionally, third party payors, regional health care 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 health care programs. We expect additional measures addressing pharmaceutical pricing to be proposed and may be adopted in the future, which could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired. In the European Union, similar political, economic and regulatory developments as those in the United States may affect our ability to profitably commercialize our products.

Finally, legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not

prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

If we or our third-party manufacturers fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We and our third-party manufacturers are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and produce hazardous waste products. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Further, with respect to the operations of our third-party contract manufacturers, it is possible that if they fail to operate in compliance with applicable environmental, health and safety laws and regulations or properly dispose of wastes associated with our products, we could be held liable for any resulting damages, suffer reputational harm or experience a disruption in the manufacture and supply of our product candidates or products.

Risks Related to Employee Matters and Managing Our Operations

We are a development-stage company with a limited number of employees and we may experience difficulties in retaining key employees and consultants.

We are a development-stage company with a total of 35 full-time employees as of January 31, 2019. These employees support key areas of our business and operations, including clinical operations, regulatory affairs, drug safety, data management, outsourced manufacturing and supply chain management, analytical development and quality assurance, as well as all of our general and administrative functions and public company infrastructure.

We remain highly dependent on David R. Guyer, M.D., our Executive Chairman, and Glenn P. Sblendorio, our Chief Executive Officer and President, as well as the other principal members of our management, scientific and clinical teams. We do not maintain "key person" insurance for any of our executives or other employees. Although we have entered into letter agreements with our executive officers, each of them and our non-executive employees may terminate their employment with us at any time. As a result, key employees that we expect to retain to assist with the growth of our business may choose not to remain employees. In addition, we may experience difficulties in retaining key employees, given the change in prospects for our company as well as other challenges. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business plan.

Furthermore, replacing any such 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 successfully develop, gain marketing approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms, if at all, given the competition among numerous pharmaceutical and biotechnology companies for similar personnel, including, in particular, personnel with gene therapy experience. 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, pipeline expansion and commercialization strategies, including

retaining key consultants previously used by Inception 4 for our HtrA1 inhibitor program and engaging and retaining key consultants with gene therapy experience. Our consultants and advisors may be employed by employers 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 strategically attract or retain high quality personnel as we implement our business plan, our ability to pursue our development strategy would be limited.

If we fail to establish and maintain effective internal control over financial reporting, our ability to accurately report our financial results could be adversely affected.

A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of the company's annual or interim financial statements would not be prevented or detected on a timely basis. If any material weakness in our internal control over financial reporting is discovered or occurs in the future, our financial statements may contain material misstatements and we could be required to restate our financial results. As previously disclosed in July 2015, our management concluded that we experienced a material weakness in internal controls related to technical accounting expertise over the accounting for deferred tax assets and income tax accounting in general during certain prior financial reporting periods. The deficiency in the application of our controls relating to technical accounting expertise over the accounting for deferred tax assets and income tax accounting in general resulted in the audit committee of our board of directors concluding that the relevant financial statements should not be relied upon, and our subsequent restatement of the relevant financial statements.

During the year ended December 31, 2015, we took the following steps to remediate the identified material weakness: we added staffing within our finance department and engaged a nationally recognized accounting firm, in each case, with technical expertise in the area of tax accounting and financial reporting. Our management concluded that the identified material weakness in internal control over financial reporting was fully remediated as of December 31, 2015. Although we have remediated this deficiency in internal control over financial reporting, we cannot be certain that the remedial measures that we took in the past or other measures we take in the future, especially in light of our decreased size as a result of the implementation of our reduction in personnel during the year ended on December 31, 2017, and the associated decrease in staffing in our accounting and finance areas, will ensure that we maintain adequate controls over our financial reporting going forward and, accordingly, additional material weaknesses could occur or be identified. Any additional material weaknesses or combination of deficiencies could materially and adversely affect our ability to provide timely and accurate financial information, and the current and future deficiencies may impact investors' confidence in our internal controls and our company, which could cause our stock price to decline.

Risks Related to Our Common Stock

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove members of our board of directors and management.

Provisions in our certificate of incorporation and our by-laws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- provide for a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board of directors;
- provide for advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our certificate of incorporation or by-laws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for stockholders.

Our stock price may be volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. The stock market in general and the market for smaller pharmaceutical and biotechnology 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, our stockholders may not be able to sell their shares of common stock at or above the price at which they purchased their shares. The market price for our common stock may be influenced by many factors, including:

- the success of products or technologies that compete with our product candidates, including results of clinical trials of product candidates of our competitors;
- results of clinical trials for our product candidates and the timing of the receipt of such results;
- the results of our efforts to in-license or acquire the rights to other products, product candidates and technologies for the treatment of ophthalmic diseases;
- political, regulatory or legal developments in the United States and other countries;
- 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;
- actual or anticipated 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; and
- the other factors described in this "Risk Factors" section.

For example, following our announcement of initial, top-line results from our OPH2007 Phase 2a clinical trial for Zimura in combination with the anti-VEGF agent Lucentis for the treatment of wet AMD, the closing price of our common stock declined from $2.22 on November 9, 2018 to $1.92 on November 14, 2018 and declined further thereafter. The closing price of our common stock was $1.45 on February 27, 2019. Following periods of volatility in the market price of a company's stock, securities class-action litigation has often been instituted against that company. We and certain of our current and former executive officers have been named as defendants in purported class action lawsuits following our announcement in December

2016 of the initial, top-line results from the first two of our Phase 3 Fovista trials for the treatment of wet AMD. See Part I, Item 3 of this Annual Report on Form 10-K and in this "Risk Factors" section, "*Risks Related to Our Business Plan, Financial Position and Need for Additional Capital—We and certain of our current and former executive officers have been named as defendants in lawsuits that could result in substantial costs and divert management's attention*." These proceedings and other similar litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business.

If a significant portion of our total outstanding shares are sold into the market, the market price of our common stock could drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, 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 common stock. We issued 5,174,727 shares of our common stock to the former equityholders of Inception 4 as upfront consideration for the Inception 4 Merger. These shares are subject to lock-up restrictions, which will expire at the end of April 2019 with respect to 50% of such shares, and at the end of October 2019 with respect to the remaining 50% of such shares, following which such shares may be freely sold and traded, subject to volume, notice and manner of sale restrictions under Rule 144 in the case of our affiliates. Moreover, we have agreed to use commercially reasonable efforts, subject to specified conditions, to register these shares, following which the volume, notice and manner of sale restrictions under Rule 144 will not apply. We may issue additional shares to the former equityholders of Inception 4 in the event that we achieve certain clinical and regulatory milestones in relation to our HtrA1 inhibitor program.

Moreover, we have filed, and expect to continue to file, registration statements on Form S-8 registering all shares of common stock that we may issue under our equity compensation plans. Once registered on Form S-8, shares underlying these equity awards can be freely sold in the public market upon issuance, subject to volume, notice and manner of sale limitations applicable to affiliates.

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

As a public company, we incur and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Select Market 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 devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and have made some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish with our periodic Exchange Act reports a report by our management on our internal control over financial reporting. We are also required to include with our annual report an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404, we must 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 and engage outside consultants to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. There is a risk that our internal control over financial reporting may, in the future, be found to be ineffective under Section 404. Our identification of one or more material weaknesses could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be our stockholders' sole source of gain.

We have never declared or paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our properties consist of office space in New York, New York and Princeton, New Jersey. We lease approximately 13,500 square feet of office space in New York, New York under a lease that terminates at the end of June 2020 and approximately 5,500 square feet of office space in Princeton, New Jersey under a sublease that terminates in March 2020.

Item 3. Legal Proceedings

On January 11, 2017, a putative class action lawsuit was filed against us and certain of our current and former executive officers in the United States District Court for the Southern District of New York, captioned Frank Micholle v. Ophthotech Corporation, et al., No. 1:17-cv-00210. On March 9, 2017, a related putative class action lawsuit was filed against us and the same group of our current and former executive officers in the United States District Court for the Southern District of New York, captioned Wasson v. Ophthotech Corporation, et al., No. 1:17-cv-01758. These cases were consolidated on March 13, 2018. On June 4, 2018, the lead plaintiff filed a consolidated amended complaint, the CAC. The CAC purports to be brought on behalf of shareholders who purchased our common stock between March 2, 2015 and December 12, 2016. The CAC generally alleges that we and certain of our officers violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements concerning the results of our Phase 2b trial and the prospects of our Phase 3 trials for Fovista in combination with anti-VEGF agents for the treatment of wet AMD. The CAC seeks unspecified damages, attorneys' fees, and other costs. We and the individual defendants filed a motion to dismiss the CAC on July 27, 2018. That motion is fully briefed.

On February 7, 2018, a shareholder derivative action was filed against the members of our board of directors in the New York Supreme Court Commercial Division, captioned Cano v. Guyer, et al., No. 650601/2018. The complaint alleges that the defendants breached their fiduciary duties to our company by adopting a compensation plan that overcompensates the non-employee members of the Board relative to boards of companies of comparable market capitalization and size. The complaint also alleges that the defendants were unjustly enriched as a result of the alleged conduct. The complaint purports to seek unspecified damages on our behalf, attorneys' fees, and other costs, as well as an order directing us to reform and improve our corporate governance and internal procedures to comply with applicable laws. We filed a motion to dismiss this case on May 14, 2018. On June 4, 2018, the plaintiff filed an amended complaint. On June 25, 2018, we filed a renewed motion to dismiss this case. On December 3, 2018, the parties filed a stipulation of settlement that contemplates that we will adopt certain compensation-related governance reforms and does not obligate the defendants or us to pay any monetary damages. In addition, we expect we may be liable to pay approximately $300,000 in fees to plaintiff's counsel. A hearing to determine whether the court will approve the settlement is scheduled for March 12, 2019.

On August 31, 2018, a shareholder derivative action was filed against current and former members of our board of directors and certain of our current and former officers in the United States District Court for the Southern District of New York, captioned Luis Pacheco v. David R. Guyer, et al., Case No. 1:18-cv-07999. The complaint, which is based substantially on the facts alleged in the CAC, alleges that the defendants breached their fiduciary duties to our company and wasted our corporate assets by failing to oversee our business, and also alleges that the defendants were unjustly enriched as a result of the alleged conduct, including through receipt of bonuses, stock options and similar compensation from us, and through sales of our stock between March 2, 2015 and December 12, 2016. The complaint purports to seek unspecified damages on our behalf, attorneys' fees, and other costs, as well as an order directing us to reform and improve our corporate governance and internal procedures to comply with applicable laws, including submitting certain proposed amendments to our corporate charter, bylaws and corporate governance policies for vote by our stockholders. On December 14, 2018, we filed a motion to dismiss the complaint. The plaintiff filed an opposition to the motion to dismiss on February 22, 2019, and our reply is due on April 3, 2019.

On October 16, 2018, our board of directors received a shareholder demand to investigate and commence legal proceedings against certain members of our board of directors. The demand alleges facts that are substantially similar to the facts alleged in the CAC and the Pacheco complaint and asserts claims that are substantially similar to the claims asserted in the Pacheco complaint. On January 30, 2019, our board of directors received a second shareholder demand from a different shareholder to investigate and commence legal proceedings against certain current and former members of our board of directors based on allegations that are substantially similar to the allegations contained in the first demand letter.

We deny any and all allegations of wrongdoing and intend to vigorously defend against these lawsuits. We are unable, however, to predict the outcome of these matters at this time. Moreover, any conclusion of these matters in a manner adverse to us and for which we incur substantial costs or damages not covered by our directors' and officers' liability insurance would have a material adverse effect on our financial condition and business. In addition, the litigation could adversely impact our reputation and divert management's attention and resources from other priorities, including the execution of our business plan and strategies that are important to our ability to grow our business, any of which could have a material adverse effect on our business.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuers Purchases of Equity Securities

Our common stock has been publicly traded on The Nasdaq Global Select Market under the symbol "OPHT" since September 25, 2013.

Holders

As of January 31, 2019, there were approximately 100 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividends

We have never declared or paid cash dividends on our common stock, and we do not expect to pay any cash dividends on our common stock in the foreseeable future.

Recent Sales of Unregistered Securities

On October 30, 2018, we issued 5,044,201 shares of our common stock to the former equityholders of Inception 4 as upfront consideration for our acquisition of Inception 4. On December 31, 2018, we issued to these same stockholders 130,526 shares of our common stock following finalization of customary post-closing adjustments under the Inception 4 Merger Agreement.

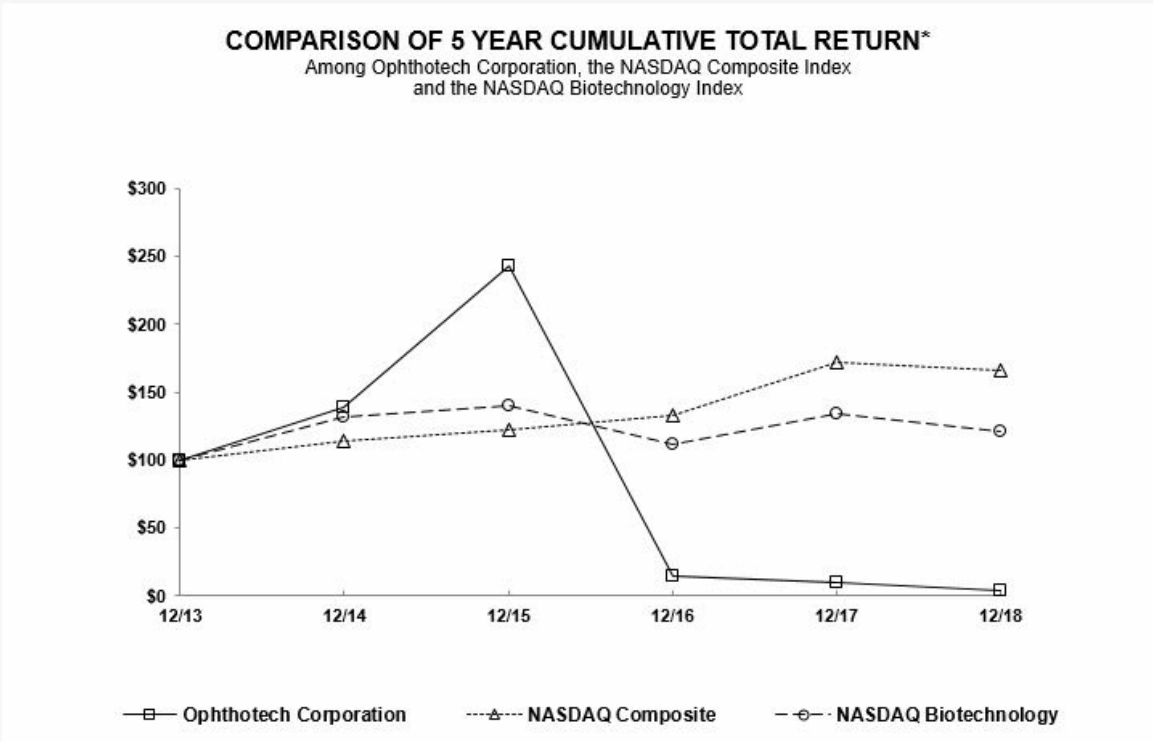
The foregoing transactions did not involve any underwriters, underwriting discounts or commissions, or any public offering, and we believe each transaction was exempt from the registration requirements of the Securities Act of 1933, as amended, or the Securities Act, in reliance upon Section 4(a)(2) thereof, and/or Regulation S or Regulation D promulgated thereunder. Except for the foregoing, there were no issuances of equity securities that were not registered under the Securities Act during the period covered by this Annual Report on Form 10-K.

Purchase of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Stock Performance Graph

The following graph and chart compares the cumulative annual stockholder return on our common stock over the period commencing December 31, 2013 and ending on December 31, 2018, to that of the total return for the NASDAQ Composite Index and the NASDAQ Biotechnology Index, assuming an investment of $100 on December 31, 2013. In calculating cumulative total annual stockholder return, reinvestment of dividends, if any, is assumed. The indices are included for comparative purposes only. They do not necessarily reflect management's opinion that such indices are an appropriate measure of the relative performance of our common stock and are not intended to forecast or be indicative of future performance of our common stock. The following graph and related information shall not be deemed "soliciting material" or be "filed" with the Securities and Exchange Commission, or SEC, nor shall such information be incorporated by reference in any of our filings under the Securities Act, or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing. We obtained information used on the graph from Research Data Group, Inc., a source we believe to be reliable.



	12/13	12/14	12/15	12/16	12/17	12/18
Ophthotech Corporation	$ 100.00	$ 138.70	$ 242.75	$ 14.93	$ 9.64	$ 3.71
NASDAQ Composite	100.00	114.62	122.81	133.19	172.11	165.84
NASDAQ Biotechnology	100.00	131.71	140.56	112.25	133.67	121.24

*$100 invested on December 31, 2013 in stock or index, including reinvestment of dividends. Fiscal year ending December 31.

Item 6. Selected Financial Data

The following selected financial data should be read together with our financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. We have derived the statements of operations data for the years ended December 31, 2018, 2017, 2016, 2015 and 2014 and the balance sheet data as of December 31, 2018, 2017, 2016, 2015 and 2014 from our audited financial statements, which have been audited by Ernst & Young LLP, an independent registered accounting firm. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period, and our results for any interim period are not necessarily indicative of results to be expected for a full fiscal year.

	Years ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands, except per share data)				
Statements of Operations Data:					
Collaboration revenue	$ —	$ 209,977	$ 50,909	$ 51,505	$ 41,259
Operating expenses:					
Research and development	41,737	66,289	196,295	131,012	88,385
General and administrative	23,612	35,683	50,178	44,021	33,387
Total operating expenses	65,349	101,972	246,473	175,033	121,772
Income (loss) from operations	(65,349)	108,005	(195,564)	(123,528)	(80,513)
Interest income (expense)	2,389	1,522	1,704	971	217
Gain on extinguishment of royalty purchase liability	125,000	—	—	—	—
Other income (expense)	(16)	(34)	34	53	—
Income (loss) before income tax provision (benefit)	62,024	109,493	(193,826)	(122,504)	(80,296)
Income tax provision (benefit)	(1,063)	(4,712)	(406)	(16,787)	36,476
Net income (loss)	63,087	114,205	(193,420)	(105,717)	(116,772)
Add: accretion of preferred stock dividends	—	—	—	—	—
Net income (loss) attributable to common stockholders	$ 63,087	$ 114,205	$ (193,420)	$ (105,717)	$ (116,772)
Net income (loss) per common share:					
Basic	$ 1.70	$ 3.18	$ (5.45)	$ (3.06)	$ (3.51)
Diluted	$ 1.70	$ 3.17	$ (5.45)	$ (3.06)	$ (3.51)
Weighted average common shares outstanding:					
Basic	37,061	35,919	35,486	34,580	33,258
Diluted	37,088	36,007	35,486	34,580	33,258

	As of December 31,				
	2018	2017	2016	2015	2014
	(in thousands)				
Balance sheets data:					
Cash, cash equivalents, and marketable securities	$ 131,201	$ 166,972	$ 289,278	$ 391,890	$ 463,560
Total assets	$ 137,165	$ 175,576	$ 299,630	$ 428,851	$ 479,786
Deferred revenue	$ —	$ —	$ 209,976	$ 213,066	$ 209,624
Royalty purchase liability	$ —	$ 125,000	$ 125,000	$ 125,000	$ 125,000
Total liabilities	$ 13,206	$ 137,535	$ 394,248	$ 368,904	$ 351,249
Additional paid-in capital	$ 545,585	$ 522,759	$ 504,517	$ 465,927	$ 428,390
Accumulated deficit	$ (421,667)	$ (484,754)	$ (598,959)	$ (405,539)	$ (299,822)
Total stockholders' equity (deficit)	$ 123,959	$ 38,041	$ (94,618)	$ 59,947	$ 128,537

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our financial condition and results of operations should be read together with our financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties and should be read together with the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a science-driven biopharmaceutical company specializing in the development of novel therapies to treat ophthalmic diseases, with a focus on age-related and orphan retinal diseases. We are seeking to leverage our development platform, clinical experience and retina expertise to develop both therapeutics and gene therapies in these disease areas. We believe gene therapy as a treatment modality holds tremendous promise for ophthalmic diseases. We also believe therapeutics will continue to serve an important role in ophthalmic drug development, particularly as treatments with novel mechanisms of action are developed and brought to market and as the long-term effects of these treatments continue to be understood. Our team has significant ophthalmic drug development experience and deep relationships with global ophthalmology thought leaders. We have an extensive network of ophthalmic clinical trial sites, having worked with over 250 sites worldwide. We believe that the combination of these factors, together with our experience in designing and executing investigational new drug, or IND, -enabling studies and clinical trials for eye diseases, and specifically back of the eye diseases, provide us a competitive advantage.

We currently have ongoing research and development programs for both therapeutics and gene therapy product candidates and technologies.

Our therapeutics portfolio consists of Zimura® (avacincaptad pegol), which is a C5 complement inhibitor, and our program of High temperature requirement A serine peptidase 1 protein, or HtrA1, inhibitors. We have Phase 2b clinical trials ongoing evaluating Zimura for the treatment of:

- geographic atrophy, or GA, which is a late-stage form of dry age-related macular degeneration, or AMD, characterized by retinal cell death and degeneration of tissue in the central portion of the retina, referred to as the macula, and which may result in loss of vision; and
- autosomal recessive Stargardt disease, or STGD1, which is an orphan inherited retinal disease, or IRD, that also may result in loss of vision.

We previously also evaluated Zimura in combination with Lucentis® (ranibizumab), an anti-vascular endothelial growth factor, or anti-VEGF, agent, for the treatment of wet AMD, for which we completed a Phase 2a clinical trial during the fourth quarter of 2018. We do not currently have plans to develop Zimura further in wet AMD. Our HtrA1 inhibitor program, which we are developing for GA secondary to dry AMD and potentially other age-related retinal diseases, such as wet AMD and idiopathic polypoidal choroidal vasculopathy, or IPCV, is in the preclinical stage of development.

Our gene therapy portfolio consists of several ongoing research and preclinical development programs that use adeno-associated virus, or AAV, for gene delivery. These AAV gene therapy programs are targeting the following orphan IRDs:

- rhodopsin-mediated autosomal dominant retinitis pigmentosa, or RHO-adRP, which is characterized by progressive and severe bilateral loss of vision leading to blindness;
- Best vitelliform macular dystrophy, or Best disease, which is characterized by bilateral egg yolk-like macular lesions that, over time, progress to atrophy and loss of vision, and potentially other diseases associated with mutations in the *Best1* gene, which we refer to as bestrophinopathies;
- Leber Congenital Amaurosis type 10, or LCA10, which is characterized by severe bilateral loss of vision at or soon after birth; and
- autosomal recessive Stargardt disease.

Therapeutic Development Programs

Zimura Clinical Programs

Zimura, our C5 complement inhibitor, is a chemically-synthesized, pegylated RNA aptamer. Aptamers are short molecules made up of a single stranded nucleic acid sequence or amino acid sequence that binds molecular targets with high selectivity and specificity. We currently have two clinical trials for Zimura ongoing. These clinical trials are designed to obtain data to guide potential future development efforts and are not intended to be pivotal studies. The following is a brief description of these trials and their current status:

- **OPH2003 (geographic atrophy (GA) secondary to dry AMD)**: an ongoing, randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy in patients with GA secondary to dry AMD. We completed enrollment for this clinical trial in October 2018 with a total of 286 patients enrolled. We expect that initial, top-line data from this clinical trial will be available during the fourth quarter of 2019.

- **OPH2005 (autosomal recessive Stargardt disease (STGD1))**: an ongoing, randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura monotherapy for the treatment of STGD1. We completed enrollment for this clinical trial in February 2019 with a total of 95 patients enrolled. We expect that initial, top-line data from this clinical trial will be available during the second half of 2020.

HtrA1 Inhibitor Program

We are pursuing the preclinical development of certain HtrA1 inhibitors, to which we acquired rights through our October 2018 acquisition of Inception 4, Inc., or Inception 4, for the treatment of GA secondary to dry AMD. Our HtrA1 inhibitor program includes a number of lead small molecule compounds that show high affinity and specificity for HtrA1 when tested, as well as a number of backup compounds. We are pursuing formulation development studies with the goal of identifying a formulation for intravitreal application in the eye. If we are successful in identifying and formulating a product candidate from this program, we plan to initiate IND-enabling activities for the selected product candidate. Based on current timelines and subject to successful completion of preclinical development, we are currently targeting submission of an IND to the U.S. Food and Drug Administration, or FDA, for a product candidate from this program for the treatment of GA secondary to dry AMD by late 2020.

Gene Therapy Research and Development Programs

RHO-adRP Product Candidate

We are pursuing the preclinical development of our novel AAV gene therapy product candidate for the treatment of RHO-adRP, to which we acquired exclusive development and commercialization rights through a June 2018 license agreement with the University of Florida Research Foundation, or UFRF, and the University of Pennsylvania, or Penn. We and Penn are conducting additional preclinical studies of the RHO-adRP product candidate and a natural history study of RHO-adRP patients. In parallel, we have commenced IND-enabling activities for the RHO-adRP product candidate, including manufacturing for preclinical toxicology studies. We have engaged a gene therapy contract development and manufacturing organization, or CDMO, as the manufacturer for preclinical and Phase 1/2 clinical supply of our RHO-adRP product candidate. Based on current timelines and subject to regulatory review, we expect to initiate a Phase 1/2 clinical trial for this product candidate during 2020.

Bestrophinopathies Program

We have an exclusive option agreement with Penn and UFRF to acquire an exclusive, global license to develop and commercialize novel AAV gene therapy product candidates for the treatment of Best disease and other bestrophinopathies. We and Penn are conducting additional preclinical studies of a product candidate from this program and natural history studies of patients with bestrophinopathies. In parallel, we are planning to commence IND-enabling activities for a product candidate from this program, including manufacturing for preclinical toxicology studies. We have recently engaged a CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of this product candidate. Based on current timelines and subject to regulatory review and execution of a definitive license agreement with Penn and UFRF, we expect to initiate a Phase 1/2 clinical trial for a product candidate from this program during 2021.

University of Massachusetts Medical School Research (LCA10 and STGD1; Gene Delivery Methods)

We are funding three sponsored research programs at the University of Massachusetts Medical School, or UMMS. Two of these programs consist of utilizing a "minigene" approach to create AAV gene therapy product candidates targeting LCA10 and STGD1. AAV vectors are generally limited as a delivery vehicle by the size of their genetic cargo, which is restricted to approximately 4,700 base pairs of genetic code. The use of "minigenes" seeks to deliver a smaller but still functional form of a larger gene packaged into a standard-size AAV delivery vector. The third program consists of evaluating various AAV gene delivery methods for potential application in the eye. UMMS has granted us an option to obtain an exclusive license to any patents or patent applications that result from any of these sponsored research programs. The sponsored research at UMMS is ongoing and we expect to receive results from the sponsored research for LCA10 during 2019, at which point we may elect to exercise our option to in-license the LCA10 program.

Business Development Activities

In 2018, we continued to implement a business development strategy, which we started to undertake in early 2017, based on reviewing our strategic alternatives in light of our deep expertise and experience in ophthalmic drug development and our business plan. Without limiting any option, the principal focus of this strategy was to actively explore obtaining rights to additional products, product candidates and technologies to treat ophthalmic diseases, particularly those in the back of the eye. These efforts have resulted in the expansion of our research and development pipeline, with the initiation of our gene therapy sponsored research programs with UMMS in February 2018, the in-license of our RHO-adRP gene therapy product candidate in June 2018, the acquisition of our HtrA1 inhibitor program in October 2018 and the entry into our exclusive option agreement with Penn and UFRF for gene therapy product candidates for bestrophinopathies in October 2018. We expect to continue to evaluate opportunities to potentially obtain rights to additional gene therapy and therapeutic product candidates on a selective basis. We intend to continue to focus on opportunities that present a compelling scientific rationale, have the potential to address an unmet medical need and present a meaningful commercial opportunity. To the extent feasible, we plan to target opportunities where we believe third-party funding for specific programs or technologies may be available.

Fovista Wind-down

In December 2016 and August 2017, we received initial top-line data from our three pivotal clinical trials, referred to as OPH1002, OPH1003 and OPH1004, evaluating the anti-platelet derived growth factor, or anti-PDGF, aptamer Fovista® (pegpleranib) administered in combination with anti-VEGF agents for the treatment of wet AMD. These top-line data indicated that the trials failed to achieve their pre-specified primary endpoints. We terminated these trials, as well as several other smaller Fovista trials in wet AMD, which we refer to as the Fovista Expansion Studies, in 2017. We have no plans for the future development of Fovista.

Prior Novartis Agreement

In May 2014, we entered into a licensing and commercialization agreement with Novartis Pharma AG, or Novartis, which we refer to as the Novartis Agreement. Under the Novartis Agreement, we granted Novartis exclusive rights under specified patent rights, know-how and trademarks controlled by us to manufacture standalone Fovista products and products combining Fovista with an anti-VEGF agent to which Novartis has rights in a co-formulated product, for the treatment, prevention, cure or control of any human disease, disorder or condition of the eye, and to develop and commercialize those licensed products in all countries outside of the United States, which we refer to as the Novartis Territory. We agreed to use commercially reasonable efforts to complete our pivotal Phase 3 clinical program for Fovista and Novartis agreed to use commercially reasonable efforts to develop a standalone Fovista product and a co-formulated product containing Fovista and an anti-VEGF agent to which Novartis has rights, and to use commercially reasonable efforts, subject to obtaining marketing approval, to commercialize licensed products in the Novartis Territory in accordance with agreed development and marketing plans. Novartis paid us a $200.0 million upfront fee upon execution of the Novartis Agreement, as well as $50.0 million upon the achievement of each of two patient enrollment-based milestones, and $30.0 million upon the achievement of a third, and final, enrollment-based milestone, for an aggregate of $330.0 million. In July 2017, we and Novartis entered into a letter agreement, which we refer to as the July 2017 Letter Agreement, to streamline the process and timeline for evaluating data from the final Fovista Phase 3 clinical trial once it became available. In October 2017, following the failure of the Phase 3 Fovista program and pursuant to the terms of the July 2017 Letter Agreement, Novartis elected to terminate the Novartis Agreement with immediate effect.

Prior Novo Agreement

In May 2013, we entered into a Purchase and Sale Agreement with Novo Holdings A/S (formerly Novo A/S and which we refer to as Novo), which we refer to as the Novo Agreement, pursuant to which we obtained financing in three tranches in an aggregate amount equal to $125.0 million in return for the sale to Novo of aggregate royalties of a mid-single-digit percentage on worldwide sales of Fovista, certain products related to Fovista, as specified in the Novo Agreement, or

Fovista-Related Products, and certain other PDGF antagonists which we might develop, as specified in the Novo Agreement, or Other Products. The three tranches of financing, in which Novo purchased three low single-digit royalty interests and paid us $125.0 million in the aggregate, closed in May 2013, January 2014 and November 2014. We recorded the aggregate $125.0 million in proceeds that we received under the Novo Agreement as a royalty purchase liability on our Balance Sheet in accordance with Accounting Standards Codification 730, *Research and Development*.

On December 31, 2018, we and Novo entered into a letter agreement, which we refer to as the Novo Termination Agreement, that terminated the Novo Agreement. As a result of the Novo Termination Agreement, Novo relinquished all rights to receive royalties based on net sales of Fovista, Fovista-Related Products and Other Products. In exchange, we agreed to forbear from any future filing, prosecution, maintenance or enforcement of any intellectual property rights related to Fovista, Fovista-Related Products or Other Products, and from granting any third party or affiliate any right or license in any such intellectual property rights or clinical study data generated by or on behalf of us, our affiliates or licensees or sublicensees, for the development, manufacture or commercialization of Fovista, Fovista-Related Products, Other Products or any other antagonists of PDGF. The foregoing restriction does not apply to gene therapies (so long as we do not grant any rights or licenses to intellectual property or clinical study data related to Fovista or Fovista-Related Products). We further agreed, until December 31, 2028, not to develop, manufacture, seek or obtain regulatory approval for or commercialize Fovista, Fovista-Related Products or Other Products without the prior written consent of Novo. The foregoing restriction does not apply to any gene therapies (so long as we do not utilize data related to Fovista or Fovista-Related Products).

Effective December 31, 2018, as a result of the Novo Termination Agreement, we extinguished the $125.0 million royalty purchase liability from our Balance Sheet as we have no legal obligation to repay Novo the $125.0 million through future product royalties or any other development activities. In addition, we recognized a related gain of $125.0 million in our Statements of Operations for the year ended December 31, 2018. The extinguishment of the royalty purchase liability and the related gain did not impact our cash balance during this period as we had received the proceeds related to the royalty purchase liability in prior periods.

Financial Matters

As of December 31, 2018, we had cash and cash equivalents of $131.2 million. We believe that our cash and cash equivalents will be sufficient to fund our operations and capital expenditure requirements as currently planned for at least the next 12 months. We estimate that our year end 2019 cash and cash equivalents will range between $80.0 million and $85.0 million. This estimate is based on our current business plan, including the continuation of our clinical development programs for Zimura, the expansion and continued preclinical development of our HtrA1 inhibitor program, and the expansion and continuation of our gene therapy research and development programs, including our ongoing collaborative gene therapy sponsored research programs. This estimate does not reflect any additional expenditures resulting from the potential in-licensing or acquisition of additional products, product candidates or technologies, including from our ongoing collaborative gene therapy sponsored research programs, or any associated development that we may pursue following any such transaction.

Our ability to become and remain profitable depends on our ability to generate revenue in excess of our expenses. We do not expect to generate significant product revenue unless, and until, we obtain marketing approval for, and commercialize, any of our product candidates, which, if we are successful, will likely take at least several years. We may be unsuccessful in our efforts to develop and commercialize these product candidates. Even if we succeed in developing and commercializing one or more of our product candidates, we may never achieve sufficient sales revenue to achieve or maintain profitability. Our capital requirements will also depend on many other factors, including whether we are successful in our pursuit to acquire or in-license and subsequently develop additional product candidates or technologies. We expect we will require substantial, additional funding in order to complete the activities necessary to develop and commercialize one or more of our product candidates. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Financial Operations Overview

Revenue

As we have no products approved for sale, we do not expect to receive any revenue related to our product candidates until we obtain regulatory approval for and commercialize such products, or until we potentially enter into agreements with third parties for the development and commercialization of our product candidates. If our development efforts for any of our product candidates result in regulatory approval or if we enter into collaboration agreements with third parties, we may generate revenue from product sales or from such third parties.

Prior to 2018, our revenue resulted from payments received under the Novartis Agreement as modified by the July

2017 Letter Agreement, both of which are described below. We completed the deliverables under the Novartis Agreement during the third quarter of 2017.

In May 2014, we received an upfront payment of $200.0 million in connection with our entry into the Novartis Agreement, which was not recorded as revenue due to the existence of a contingency with respect to our right to terminate the agreement in certain circumstances and the associated termination fee equivalent to the entire $200.0 million upfront payment, which we would have been required to repay if we elected to exercise this termination option. In each of September 2014 and March 2015, we achieved a $50.0 million enrollment-based milestone, and in June 2016, we achieved a $30.0 million enrollment-based milestone, for an aggregate total of $130.0 million in milestones, under the Novartis Agreement. We used the relative selling price method to allocate these payments to contract deliverables based on our performance obligations under the Novartis Agreement.

The July 2017 Letter Agreement resolved the contingency with respect to our termination right, allowing us to immediately recognize as revenue the portion of the upfront payment allocated using the relative selling price method to deliverables completed during prior periods. During the third quarter of 2017, we completed the remaining deliverables under the Novartis Agreement and the July 2017 Letter Agreement and recognized as revenue the balance of all of the payments previously received from Novartis related to licensing, research and development, manufacturing and joint operating committee activities that had been previously deferred using the relative selling price method. In total, during the third quarter of 2017, we recognized $206.7 million in previously deferred collaboration revenue in connection with the Novartis Agreement. The recognition of this revenue during the period did not impact our cash balance. In October 2017, following the failure of the Fovista Phase 3 program and pursuant to the terms of the July 2017 Letter Agreement, Novartis elected to terminate the Novartis Agreement with immediate effect.

Below is a summary of the components of our collaboration revenue for the years ended December 31, 2018, 2017 and 2016:

	Years ended December 31,		
	2018	2017	2016
		(in thousands)	
License revenue	$ —	$ 152,912	$ 22,937
Research and development activity revenue	—	56,180	9,741
API transfer revenue	—	754	18,212
Joint operating committee revenue	—	131	19
Total collaboration revenue	$ —	$ 209,977	$ 50,909

Research and Development Expenses

Our research and development expenses primarily consist of costs associated with the manufacturing, development, and clinical testing of Zimura and, historically, Fovista, as well as costs associated with the preclinical development of other product candidates, formulations and technologies, including costs associated with our HtrA1 inhibitor program, costs associated with our RHO-adRP gene therapy product candidate, including related sponsored research with Penn, costs associated with the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling studies, and costs associated with our ongoing gene therapy sponsored research programs with UMMS. Our research and development expenses consist of:

- external research and development expenses incurred under arrangements with third parties, such as academic research collaborators, contract research organizations, or CROs, and other vendors and contract manufacturing organizations, or CMOs, for the production of drug substance and drug product; and

- employee-related expenses for employees dedicated to research and development activities, including salaries, benefits and share-based compensation expense.

Research and development expenses also include costs of acquired product licenses, in-process research and development, and related technology rights where there is no alternative future use, costs of prototypes used in research and development, consultant fees and amounts paid to collaborative partners.

All research and development expenses are charged to operations as incurred in accordance with Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, 730, *Research and Development*, or ASC 730. We account for non-refundable advance payments for goods and services that will be used in future research and development

activities as expenses when the service has been performed or when the goods have been received, rather than when the payment is made. To date, the large majority of our research and development activity has been related to Fovista and Zimura. We do not currently utilize a formal time allocation system to capture expenses on a project-by-project basis because we record expenses by functional department. Accordingly, we do not allocate expenses to individual projects or product candidates, although we do allocate some portion of our research and development expenses by functional area and by compound, as shown below.

The following table summarizes our research and development expenses for the years ended December 31, 2018, 2017 and 2016:

	Years ended December 31,		
	2018	2017	2016
	(in thousands)		
Zimura	$ 17,109	$ 11,986	$ 7,400
HtrA1	6,900	—	—
RHO-adRP	1,921	—	—
Other gene therapy research	2,008	—	—
Fovista	(358)	21,698	129,661
Personnel-related	6,088	19,413	26,700
Share-based compensation	4,967	11,114	21,380
Other	3,102	2,078	11,154
	$ 41,737	$ 66,289	$ 196,295

We expect our research and development expenses to increase as we pursue the development of Zimura, our HtrA1 inhibitor program, our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidates for which we hold an option from Penn and UFRF. We also expect to incur research and development expenses in connection with our collaborative gene therapy sponsored research programs. As we pursue our ongoing and planned Zimura, HtrA1 inhibitor, RHO-adRP and BEST1 development programs and our collaborative gene therapy sponsored research programs, or as we commence any new development efforts in relation to additional product candidates we may in-license or acquire as we pursue our business plan, we expect that our overall research and development expenses will increase from the current level of expenditure.

Our costs may exceed our expectations due to unforeseen or other reasons. For example, our costs may exceed our expectations if we experience any unforeseen issue in our ongoing clinical trials, such as delays in enrollment or issues with the availability of drug supply, or in our preclinical development programs, such as inability to develop formulations or if we experience issues with manufacturing, or if we further expand the scope of our clinical trials, preclinical development programs or collaborative gene therapy sponsored research programs. Our costs may also exceed our expectations for other reasons, for example, if we are required by the FDA, the EMA or regulatory authorities in other jurisdictions to perform clinical or nonclinical trials or other studies in addition to those we currently expect to conduct, if we experience issues with process development, establishing or scaling-up of manufacturing activities or activities to enable and qualify second source suppliers, or if we decide to increase preclinical and clinical research and development activities or build internal research capabilities or pursue internal research efforts.

The future development of our product candidates is highly uncertain. We expect the development of our product candidates will continue for at least the next several years. At this time, we cannot reasonably estimate the remaining costs necessary to complete development, to complete process development and manufacturing scale-up and validation activities and to potentially seek marketing approval with respect to our product candidates.

The successful development of our product candidates is subject to numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress and costs of our research and development activities, including manufacturing activities;
- the potential benefits of our product candidates over other therapies;
- preclinical development results and clinical trial results;
- the terms and timing of regulatory approvals;

- our ability to market, commercialize and achieve market acceptance for any of our product candidates; and
- our ability to successfully file, prosecute, defend and enforce patent claims and other intellectual property rights, together with associated expenses.

A change in the outcome of any of these variables with respect to the development of our product candidates could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if regulatory authorities were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate, we could be required to expend significant additional financial resources and time on the completion of clinical development.

See the "Liquidity and Capital Resources" section of this Item 7 of this Annual Report on Form 10-K for more information regarding our current and future financial resources and our expectations regarding our research and development expenses and funding requirements.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs for personnel, including share-based compensation expense, in our executive, legal, finance, business development, human resources, investor relations and information technology functions. Other general and administrative expenses include facility costs and professional fees for legal, including patent-related, services and expenses, consulting and accounting services, and travel expenses.

Interest Income

We currently have invested our cash and cash equivalents in money market funds and investment-grade corporate debt securities, which generate a nominal amount of interest income.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued research and development expenses, revenue recognition, share-based compensation and income taxes described in greater detail below. We base our estimates on our limited 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. Actual results may differ from these estimates under different assumptions or conditions.

Our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this Annual Report on Form 10-K. Of those policies, we believe that the following accounting policies are the most critical to aid our stockholders in fully understanding and evaluating our financial condition and results of operations.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses are related to expenses incurred with respect to academic research collaborators, CROs, CMOs and other vendors in connection with research and development and manufacturing activities.

We base our expenses related to academic research collaborators, CROs and CMOs on our estimates of the services received and efforts expended pursuant to quotations and contracts with such vendors that conduct research and development and manufacturing activities on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors

will exceed the level of services provided and result in a prepayment of the applicable research and development or manufacturing expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in us reporting amounts that are too high or too low in any particular period. There have been no material changes in estimates for the periods presented in this Annual Report on Form 10-K.

Revenue Recognition—Collaboration Revenue

Prior to 2018, our revenue resulted from payments received under the Novartis Agreement as modified by the July 2017 Letter Agreement, both of which are described below under "—Liquidity and Capital Resources—Prior Licensing and Commercialization Agreement with Novartis Pharma AG." We used the relative selling price method to allocate arrangement consideration to our performance obligations under the Novartis Agreement. We completed the deliverables under the Novartis Agreement during the third quarter of 2017.

As we have no products approved for sale, we do not expect to receive any revenue from product candidates that we develop until we obtain regulatory approval and commercialize such products, or until we potentially enter into agreements with third parties for the development and commercialization of our product candidates. If our development efforts for any of our product candidates result in regulatory approval or if we enter into collaboration agreements with third parties, we may generate revenue from product sales or from such third parties.

In the future, we will evaluate revenue contracts and arrangements, if any, following the provisions of the FASB ASC, *Revenue from Contracts with Customers (Topic 606)*, or ASC 606.

Royalty Purchase Liability

Prior to the termination of the Novo Agreement on December 31, 2018, the proceeds from the financing we received under the Novo Agreement were recorded as a royalty purchase liability on our Balance Sheet in accordance with ASC 730. Although there was no explicit repayment obligation contained in the Novo Agreement, because there was a significant related party relationship between us and Novo at the time the Novo Agreement was entered into, we treated our obligation to make royalty payments under the Novo Agreement as an implicit obligation to repay the funds advanced by Novo, and thus recorded the proceeds as a royalty purchase liability on our Balance Sheet. We extinguished this royalty purchase liability from our Balance Sheet as of December 31, 2018 when the termination of the Novo Agreement became effective.

Share-Based Compensation

We account for all share-based compensation payments issued to employees, non-employee directors, and consultants by estimating the fair value of each equity award. Accordingly, share-based compensation expense is measured based on the estimated fair value of the awards on the date of grant, net of forfeitures. We recognize compensation expense for the portion of the award that is ultimately expected to vest over the period during which the recipient renders the required services to us on a straight-line basis. In accordance with authoritative guidance, we re-measure the fair value of consultant share-based awards as the awards vest, and recognize the resulting value, if any, as expense during the period when the related services are rendered.

We apply the fair value recognition provisions of ASC 718, *Compensation—Stock Compensation*. Determining the amount of share-based compensation to be recorded requires us to develop estimates of the fair value of stock options as of their grant date. We recognize share-based compensation expense ratably over the requisite service period, which in most cases is the vesting period of the award. For grants containing performance-based vesting provisions, expense is recognized over the estimated achievement period. Calculating the fair value of share-based awards requires us to make highly subjective assumptions.

We use the Black-Scholes option pricing model to value our stock option awards and the options to purchase shares under our employee stock purchase plan. Use of this valuation methodology requires that we make assumptions as to the volatility of our common stock, the expected term of our stock options, and the risk-free interest rate for a period that approximates the expected term of our stock options and the expected dividend yield of our common stock. As a recent public company, we do not have sufficient history to estimate the volatility of our common stock price or the expected life of the options. We calculate expected volatility based on reported data for similar publicly traded companies for which historical

information is available and will continue to do so until the historical volatility of our common stock is sufficient to measure expected volatility for future option grants.

We use the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term of stock option grants to employees as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term of stock options granted to employees. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no current intention to pay cash dividends. The weighted-average assumptions used to estimate grant date fair value of stock options using the Black-Scholes option pricing model were as follows for the years ended December 31, 2018, 2017 and 2016:

	Years ended December 31,		
	2018	2017	2016
Expected common stock price volatility	85%	81%	71%
Risk-free interest rate	2.39% - 2.95%	1.82% - 2.38%	1.14% - 2.37%
Expected term of options (years)	6.0	6.1	6.1
Expected dividend yield	—	—	—

We estimate the fair value of restricted stock units, or RSUs, granted to employees using the closing market price of our common stock on the date of grant.

We also estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from our estimates. We use historical data to estimate pre-vesting forfeitures and record share-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from our estimates, the difference is recorded as a cumulative adjustment in the period when the estimates were revised.

Share-based compensation expense for equity grants to employees, non-employee directors and consultants was $11.1 million, $18.2 million and $31.7 million for the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018, we had $12.4 million of total unrecognized share-based compensation expense, which we expect to recognize over a weighted-average remaining vesting period of approximately 2.0 years. We expect our share-based compensation expense for our equity awards to employees, non-employee directors and consultants to decrease as a result of a decrease in our common stock fair value.

For the years ended December 31, 2018, 2017 and 2016, we allocated share-based compensation as follows:

	Years ended December 31,		
	2018	2017	2016
	(in thousands)		
Research and development	$ 4,967	$ 11,114	$ 21,380
General and administrative	6,105	7,057	10,280
Total	$ 11,072	$ 18,171	$ 31,660

Income Taxes

In December 2017, the U.S. Tax Cuts and Jobs Act, or the TCJA, was enacted reducing the corporate tax rate from 35% to 21% effective for tax years beginning on or after January 1, 2018. Additionally, under the TCJA, the Corporate Alternative Minimum Tax, or AMT, was repealed. Accordingly, our previously recorded AMT credits of approximately $3.5 million became refundable over a four-year period beginning in 2018 and the previously recorded valuation allowance for these AMT credits was reversed during the fourth quarter of 2017 as a result of the TCJA.

The deferred tax assets associated with our losses incurred in 2018 have a full valuation allowance recorded against them due to our history of losses and the lack of other positive evidence to support future taxable income against which these losses could be applied. See Note 9 to our financial statements in Part IV, Item 15 of this Annual Report on Form 10-K for further information regarding our expectations with respect to our income tax provision.

We are projecting a tax loss for 2018, none of which may be carried back to any prior taxable years. Although we recognized income under GAAP, during 2018 and 2017, this income is primarily due to the Novo Termination Agreement and the Novartis July 2017 Letter Agreement, which had previously been recorded on our federal and state income tax returns. This recognition of income resulted in the reduction of a deferred tax asset that was completely offset by a previously recorded

valuation allowance. With respect to the remaining deferred tax assets, except for the AMT credits previously discussed above, there was no change in the amount of assets realizable at December 31, 2018.

Results of Operations

Comparison of Years Ended December 31, 2018 and 2017

	Years ended December 31,		Increase (Decrease)
	2018	2017	
	(in thousands)		
Statements of Operations Data:			
Collaboration revenue	$ —	$ 209,977	$ (209,977)
Operating expenses:			
Research and development	41,737	66,289	(24,552)
General and administrative	23,612	35,683	(12,071)
Total operating expenses	65,349	101,972	(36,623)
Income (loss) from operations	(65,349)	108,005	(173,354)
Interest income	2,389	1,522	867
Gain on extinguishment of royalty purchase liability	125,000	—	125,000
Other expense	(16)	(34)	(18)
Income before income tax provision	62,024	109,493	(47,469)
Income tax benefit	(1,063)	(4,712)	(3,649)
Net income	$ 63,087	$ 114,205	$ (51,118)

Collaboration Revenue

We did not recognize any collaboration revenue for the year ended December 31, 2018, a decrease of $210.0 million compared to $210.0 million for the year ended December 31, 2017. Collaboration revenue for the year ended December 31, 2018 decreased as we completed all deliverables required under the Novartis Agreement and the July 2017 Letter Agreement during the year ended December 31, 2017.

Collaboration revenue for the year ended December 31, 2017 was related to the activities performed under the Novartis Agreement during such year. We completed the remaining deliverables under the Novartis Agreement and the July 2017 Letter Agreement and recognized as revenue the balance of all of the payments previously received from Novartis related to licensing, research and development, manufacturing and joint operating committee activities that had been previously deferred using the relative selling price method. In total, during the third quarter of 2017, we recognized $206.7 million in previously deferred collaboration revenue in connection with the Novartis Agreement. The recognition of this revenue during this period did not impact our cash balance. All activities under the Novartis Agreement were completed prior to the adoption of ASC 606.

Research and Development Expenses

Our research and development expenses were $41.7 million for the year ended December 31, 2018, a decrease of $24.6 million compared to $66.3 million for the year ended December 31, 2017. The decrease in research and development expenses for the year ended December 31, 2018 was primarily due to a $22.1 million decrease in costs associated with our Fovista program, including our Fovista Phase 3 clinical program and our Fovista Expansion Studies and a $19.5 million decrease in personnel costs. The decreased costs for our Fovista program included lower costs related to Fovista manufacturing activities and lower clinical trial costs as a result of the wind-down of Fovista Phase 3 clinical trials and the Fovista Expansion Studies. The decrease in personnel costs included a $6.1 million decrease in share-based compensation costs and a $4.9 million decrease in severance costs as a result of our reduction in force completed during 2017. This overall decrease was offset by the immediate expensing of $6.9 million related to our HtrA1 inhibitor program in-process research and development acquired through our Inception 4 acquisition, a $5.1 million increase in costs associated with our Zimura program and a $3.9 million increase in costs resulting from the initiation of our gene therapy programs. The increase in costs for our Zimura program related to our clinical trial activities as a result of the initiation of our OPH2005 trial, the advancement of our OPH2003 trial and the completion of our OPH2007 trial. These increased trial costs were partially offset by a decrease in Zimura manufacturing activities.

General and Administrative Expenses

Our general and administrative expenses were $23.6 million for the year ended December 31, 2018, a decrease of $12.1 million, compared to $35.7 million for the year ended December 31, 2017. The decrease in general and administrative expenses was primarily due to a decrease in costs to support our operations and infrastructure as a result of our reduction in personnel and the termination of facilities leases completed during 2017. General and administrative expenses for the year ended December 31, 2017 include approximately $6.5 million in costs related to our previously announced reduction in force and the termination of facilities leases.

Interest Income

Interest income for the year ended December 31, 2018 was $2.4 million compared to interest income of $1.5 million for the year ended December 31, 2017. The increase in interest income earned during the year ended December 31, 2018 was the result of an increase in interest rates and a change in the mix of our investment portfolio, which previously only included investments in money market funds and now includes investment in certain investment-grade corporate debt securities with original maturities of 90 days or less, offset by a decrease in cash balances available for investment.

Gain on Extinguishment of Royalty Purchase Liability

On December 31, 2018 we entered into the Novo Termination Agreement, which terminated the Novo Agreement. As we have no legal obligation to repay Novo the $125.0 million through future product royalties or any other development activities, we extinguished the $125.0 million royalty purchase liability from our Balance Sheet as of December 31, 2018 and recognized a related gain of $125.0 million in our Statements of Operations for the year ended December 31, 2018. This gain on extinguishment of the royalty purchase liability did not impact our cash balance during this period as we had received the proceeds related to the royalty purchase liability in prior periods.

Income Tax Benefit

During the year ended December 31, 2018, we recorded a benefit from income taxes of approximately $1.1 million, which primarily related to the settlement of a local tax audit.

During the year ended December 31, 2017, we recorded a benefit from income taxes of approximately $4.7 million, which primarily related to a $3.5 million reduction in our valuation allowances for AMT credits to reflect the impact of the TCJA enactment and the settlement of a franchise tax audit for $1.4 million partially offset by the reversal of previously recorded benefits related to the change in unrealized gains of our investment portfolio.

Although we had net income before income taxes during 2018 and 2017, this income is primarily due to the Novo Termination Agreement and July 2017 Letter Agreement with Novartis. Payments received under the Novo Agreement and the Novartis Agreement had previously been recorded as revenue on our federal and state income tax returns during the periods in which the payments were received. The recognition of income for financial statement purposes resulted in the reduction of a deferred tax asset that was completely offset by a previously recorded valuation allowance. With respect to the remaining deferred tax assets, except for the AMT credits discussed above, there was no change in the amount of assets realizable at December 31, 2018.

Comparison of Years Ended December 31, 2017 and 2016

	Years ended December 31,		Increase (Decrease)
	2017	2016	
	(in thousands)		
Statements of Operations Data:			
Collaboration revenue	$ 209,977	$ 50,909	$ 159,068
Operating expenses:			
Research and development	66,289	196,295	(130,006)
General and administrative	35,683	50,178	(14,495)
Total operating expenses	101,972	246,473	(144,501)
Income (loss) from operations	108,005	(195,564)	(303,569)
Interest income	1,522	1,704	(182)
Other income (expense)	(34)	34	(68)
Income (loss) before income tax benefit	109,493	(193,826)	(303,319)
Income tax benefit	(4,712)	(406)	4,306
Net income (loss)	$ 114,205	$ (193,420)	$ (307,625)

Collaboration Revenue

Collaboration revenue for the year ended December 31, 2017 was $210.0 million, an increase of $159.1 million compared to $50.9 million for the year ended December 31, 2016. Collaboration revenue for the year ended December 31, 2017 increased as we completed all deliverables required under the Novartis Agreement during 2017. The July 2017 Letter Agreement resolved the contingency with respect to our right to terminate the agreement in the event that the parties were prevented from materially progressing the development or commercialization of Fovista products for a specified period as a result of specified governmental actions, along with the associated termination fee equivalent to the entire $200.0 million upfront payment, which we would have been required to repay if we elected to exercise this termination option. We had previously deferred the entire $200.0 million upfront payment based on this contingency. As a result of our entry into the July 2017 Letter Agreement and resolution of the contingency, we immediately recognized the revenue attributable to deliverables completed during prior periods. Furthermore, as our remaining deliverables under the Novartis Agreement and the July 2017 Letter Agreement were completed during the third quarter of 2017, we recognized all of the remaining collaboration revenue previously deferred under the Novartis Agreement. Using the relative selling price method, we recognized $152.9 million related to the license we granted to Novartis under the Novartis Agreement, $56.2 million related to the research and development activities we performed under the Novartis Agreement, $0.8 million related to Fovista API we previously transferred to Novartis, and $0.1 million related to our joint operating committee participation obligations.

Collaboration revenue for the year ended December 31, 2016 was $50.9 million, of which $22.9 million was allocated to the license delivered to Novartis under the Novartis Agreement, $9.7 million was allocated to research and development activities performed under the Novartis Agreement and $18.2 million related to Fovista API we transferred to Novartis, and a de minimis amount of revenue was associated with our joint operating committee participation obligations during the same period.

Research and Development Expenses

Our research and development expenses were $66.3 million for the year ended December 31, 2017, a decrease of $130.0 million compared to $196.3 million for the year ended December 31, 2016. Research and development expenses for the year ended December 31, 2017 include approximately $7.5 million in costs related to our previously announced reduction in personnel. The decrease in research and development expenses for the year ended December 31, 2017 was primarily due to a $107.1 million decrease in costs associated with our Fovista program, including our Fovista Phase 3 clinical program and our Fovista Expansion Studies, a $6.2 million decrease in professional services and consulting fees, and a $10.3 million decrease in share-based compensation costs. The decreased costs for our Fovista program included lower costs related to Fovista manufacturing activities and lower clinical trial costs as a result of the wind-down of the OPH1002 and OPH1003 trials and the Fovista Expansion Studies. This overall decrease was offset by a $4.6 million increase associated with our Zimura programs, primarily related to manufacturing expenses.

General and Administrative Expenses

Our general and administrative expenses for the year ended December 31, 2017 were $35.7 million, a decrease of $14.5 million, compared to $50.2 million for the year ended December 31, 2016. General and administrative expenses for the year ended December 31, 2017 include approximately $5.6 million in costs related to our previously announced reduction in force and the termination of facilities leases. The decrease in general and administrative expenses was primarily due to a decrease in costs to support our operations and infrastructure offset by the additional severance and lease termination costs.

Interest Income

Interest income for the year ended December 31, 2017 was $1.5 million compared to interest income of $1.7 million for the year ended December 31, 2016. The decrease in interest income earned during the year ended December 31, 2017 was the result of a decrease in our cash and cash equivalent balances available for investment.

Income Tax Benefit

During the year ended December 31, 2017, we recorded a benefit from income taxes of approximately $4.7 million, which primarily related to a $3.5 million reduction in our valuation allowances for AMT credits to reflect the impact of the TCJA enactment and the settlement of a franchise tax audit for $1.4 million partially offset by the reversal of previously recorded benefits related to the change in unrealized gains of our investment portfolio. Although we had $109.5 million of net income before income taxes for the year ended December 31, 2017 as a result of the recognition of deferred revenue under the Novartis Agreement, we had a net loss for tax purposes for 2017 with minimal taxes due. For tax purposes, we treated payments received under the Novartis Agreement as revenue at the time the payments were received and the related deferred tax assets had a full valuation recorded against them.

During the year ended December 31, 2016, we recorded a benefit from income taxes of approximately $0.4 million, which related to unanticipated refunds received and the reduction in our valuation allowances to reflect the income tax associated with unrealized gains in our investment portfolio.

Liquidity and Capital Resources

Sources of Liquidity

Since inception, we have financed our operations primarily through private placements of our preferred stock, venture debt borrowings, funds received under the Novo Agreement, our initial public offering, which we closed in September 2013, our follow-on public offering, which we closed in February 2014, and funds we received under the Novartis Agreement. Furthermore, as a result of our acquisition of Inception 4, we obtained approximately $6.1 million in cash, which we believe will be sufficient to fund the substantial majority of anticipated development costs associated with our HtrA1 inhibitor program through the IND submission stage. In August 2018, we filed a universal shelf registration statement on Form S-3 with the SEC to register for sale from time to time up to $150.0 million of common stock, preferred stock, debt securities, depositary shares, warrants and/or units in one or more registered offerings. The shelf registration statement was declared effective on August 15, 2018. Further, in August 2018, we entered into a Sales Agreement, or the ATM Agreement, with Cowen and Company, LLC, or Cowen, pursuant to which, from time to time, we may offer and sell through Cowen shares of our common stock having aggregate gross proceeds of up to $50.0 million, subject to the terms and conditions described in the ATM agreement and SEC rules and regulations. We have not yet issued and sold any shares of our common stock under the ATM Agreement.

Cash Flows

As of December 31, 2018, we had cash and cash equivalents totaling $131.2 million and no debt. We primarily invest our cash and cash equivalents in money market funds and certain investment-grade corporate debt securities.

The following table shows a summary of our cash flows for the years ended December 31, 2018, 2017 and 2016:

	Years ended December 31,		
	2018	2017	2016
	(in thousands)		
Net cash (used in) provided by:			
Operating Activities	$ (41,911)	$ (121,821)	$ (108,596)
Investing Activities	—	154,792	13,731
Financing Activities	6,140	71	6,934
Net change in cash and cash equivalents	$ (35,771)	$ 33,042	$ (87,931)

Cash Flows from Operating Activities

Net cash used in operating activities for the year ended December 31, 2018 was $41.9 million and relates primarily to net cash used to fund our Zimura clinical trials and support the acquisition and preclinical development activities of our HtrA1 inhibitor program and our gene therapy programs.

Net cash used in operating activities for the year ended December 31, 2017 was $121.8 million and related primarily to net cash used for the wind-down of OPH1002 and OPH1003 clinical trials and the Fovista Expansion Studies, implementation of a previously announced reduction in personnel and related costs, and cancellation fees related to manufacturing commitments, as well as continuation of our OPH1004 trial through initial, top-line data in August 2017 and wind-down thereafter, and general and administrative and corporate infrastructure expenses.

See "—Funding Requirements" below for a description of how we expect to use our cash for operating activities in future periods.

Cash Flows from Investing Activities

We had no net cash provided by investing activities for the year ended December 31, 2018 was $0.0 million and relates primarily to cash acquired from our Inception 4 acquisition. Net cash provided by investing activities for the year ended December 31, 2017 was $154.8 million and relates primarily to proceeds from the maturity of marketable securities totaling $166.8 million offset by purchases of marketable securities totaling $12.0 million.

Cash Flows from Financing Activities

Net cash provided by financing activities for the year ended December 31, 2018 was $6.1 million and relates primarily to cash acquired from our Inception 4 acquisition in exchange for our common stock. Net cash provided by financing activities for the year ended December 31, 2017 was $0.1 million and related to the proceeds from stock option plan exercises and purchases made under our employee stock purchase plan.

Funding Requirements

Our product candidate Zimura is in clinical development, our HtrA1 inhibitor program, our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling activities are each in preclinical development, and we are funding sponsored research programs that are ongoing at UMMS and Penn. We expect our research and development expenses to increase as we pursue our research and development programs, as currently planned. We could also incur additional research and development expenses as we evaluate and potentially in-license or acquire, and undertake development of additional product candidates, including any promising product candidates that emerge from our collaborative gene therapy sponsored research programs. Furthermore, if we successfully develop and obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. We are party to agreements with Archemix with respect to Zimura, the former equityholders of Inception 4 with respect to our HtrA1 inhibitor program and UFRF and Penn with respect to our RHO-adRP gene therapy product candidate, in each case, that impose significant milestone payment obligations on us in connection with our achievement of specified clinical, regulatory and commercial milestones with respect to these product candidates or programs, as well as certain royalties on net sales with respect to our RHO-adRP gene therapy product candidate. It is likely that any future in-licensing or acquisition agreements that we enter into with respect to additional products, product candidates or technologies, including any definitive license agreement for the BEST1 product candidates for which we hold an option from Penn and UFRF, would include similar obligations.

We expect that we will continue to incur significant expenses as we:

- continue the clinical development of Zimura as currently planned, including, if either of our ongoing trials for Zimura support it, by pursuing additional development;
- continue the preclinical and, potentially, clinical development of our HtrA1 inhibitor program, our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidate for which we are planning to commence IND-enabling activities;
- pursue our collaborative gene therapy sponsored research programs;
- in-license or acquire the rights to, and pursue the development of, other products, product candidates or technologies;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, manufacturing, quality control, quality assurance and scientific personnel, especially as we increase our internal gene therapy capabilities or if we are successful in progressing the preclinical or clinical development of any of our product candidates or in acquiring or in-licensing rights to additional products, product candidates or technologies;
- seek marketing approval for any product candidates that successfully complete clinical trials;
- expand our outsourced manufacturing activities or establish commercial operations or sales, marketing and distribution capabilities, if we receive, or expect to receive, marketing approval for any of our product candidates; and
- expand our general and administrative functions to support future growth of the company.

As of December 31, 2018, we had cash and cash equivalents of $131.2 million. We believe that our cash and cash equivalents will be sufficient to fund our operations and capital expenditure requirements as currently planned for at least the next 12 months. We estimate that our year end 2019 cash and cash equivalents will range between $80.0 million and $85.0 million. This estimate is based on our current business plan, including the continuation of our clinical development programs for Zimura, the expansion and continued preclinical development of our HtrA1 inhibitor program, and the expansion and continuation of our gene therapy research and development programs, including our ongoing collaborative gene therapy sponsored research programs. This estimate does not reflect any additional expenditures resulting from the potential in-licensing or acquisition of additional products, product candidates or technologies, including from our ongoing collaborative gene therapy sponsored research programs, or any associated development that we may pursue following any such transaction. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

Although the future development of our product candidates is highly uncertain, we expect we will require substantial, additional funding in order to complete the activities necessary to develop and commercialize one or more of our product candidates. We expect the development of our product candidates will continue for at least the next several years. At this time, we cannot reasonably estimate the remaining costs necessary to complete development, to complete process development and manufacturing scale-up and validation activities and to potentially seek marketing approval with respect to our product candidates.

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

- the scope, progress, costs and results of our ongoing Zimura clinical programs, as well as any additional clinical trials we undertake to obtain data sufficient to seek marketing approval for Zimura in any indication;
- the scope, progress, costs and results of our efforts to develop our HtrA1 inhibitor program, including formulation development and other preclinical development activities;
- the scope, progress, costs and results of our efforts to develop our RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidate for which are planning to commence IND-enabling activities, including activities to establish manufacturing capabilities and preclinical testing to enable us to file INDs for these product candidates;

- the costs and timing of process development, manufacturing scale-up and validation activities and stability studies associated with our product candidates;
- the extent to which we in-license or acquire rights to, and undertake research or development of, additional products, product candidates or technologies, including any product candidates or other technologies we may evaluate as part of our collaborative gene therapy sponsored research programs;
- the amount of any upfront, milestone payments and other financial obligations associated with the in-license or acquisition of other product candidates;
- the scope, progress, results and costs of preclinical development and/or clinical trials for any other product candidates that we may develop;
- our ability to establish collaborations on favorable terms, if at all;
- the costs, timing and outcome of regulatory filings and reviews of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending intellectual property-related claims;
- the timing, scope and cost of commercialization activities for any of our product candidates if we receive, or expect to receive, marketing approval for a product candidate; and
- subject to receipt of marketing approval, net revenue received from commercial sales of any of our product candidates, after milestone payments and royalty payments that we would be obligated to make.

We do not have any committed external source of funds. Our ability to raise adequate additional financing when needed, and on terms acceptable to us, will depend on many factors. These factors include investors' perceptions of the potential success of our ongoing business activities, including the development of our product candidates and other programs, and the potential future growth of our business. Additionally, these factors include general market conditions that also affect other companies. These factors may make raising capital difficult, and may result in us accepting terms that are unfavorable to us, especially if we are in need of financing at the particular time. The size of our company and our status as a company listed on The Nasdaq Stock Market, or Nasdaq, may also limit our ability to raise financing. For example, our ability to raise adequate financing through a public offering may be limited by market conditions and SEC rules based on our current market capitalization. Nasdaq listing rules also generally limit the number of shares we may issue in a private placement to a number less than 20% of the number of shares of our common stock outstanding immediately prior to the transaction, unless we obtain shareholder approval, which can be expensive and time-consuming and can add risk to our ability to complete the financing transaction. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate the development of our product candidates, our collaborative gene therapy sponsored research programs, or our future commercialization efforts.

In addition, we may require additional funding beyond what we currently expect due to unforeseen or other reasons. For example, our costs may exceed our expectations if we experience any unforeseen issue in our ongoing clinical trials, such as delays in enrollment or issues with the availability of drug supply, or in our preclinical development programs, such as inability to develop formulations or if we experience issues with manufacturing, or if we further expand the scope of our clinical trials, preclinical development programs or collaborative gene therapy sponsored research programs. Our costs may also exceed our expectations for other reasons, for example, if we are required by the FDA, the EMA or regulatory authorities in other jurisdictions to perform clinical or nonclinical trials or other studies in addition to those we currently expect to conduct, if we experience issues with process development, establishing or scaling-up of manufacturing activities or activities to enable and qualify second source suppliers, or if we decide to increase preclinical and clinical research and development activities or build internal research capabilities or pursue internal research efforts. As a result, we may need or may seek to obtain additional funding for our continuing operations sooner or in greater amounts than expected.

Our need for additional financing may continue even if we are able to successfully develop one or more of our product candidates. Our future commercial revenues, if any, will be derived from sales of such product candidates, which may not be available for at least several years following completion of successful product development, if at all. In addition, if approved, our product candidates may not achieve commercial success. Even if those products are successful and we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Under most, if not all, of the foregoing circumstances, we may need to obtain substantial additional financing to achieve our business objectives.

Until such time, if ever, when we can generate substantial product revenues, we may need or may seek to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our existing stockholders' ownership interests would be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect our existing stockholders' rights as common stockholders. The dilutive effect of future capital raises may be substantial, depending on the price of our common stock at the time of such capital raise, with a lower stock price translating to greater dilution for existing stockholders. 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. In addition, we may issue equity securities as consideration for further business development transactions, which may also dilute our existing stockholders' ownership interests.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, products 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 grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Archemix C5 License Agreement

In September 2011, we entered into the C5 License Agreement with Archemix relating to anti-C5 aptamers. In connection with the C5 License Agreement, as amended, we paid Archemix an upfront licensing fee of $1.0 million and issued to Archemix an aggregate of 2,000,000 shares of our series A-1 preferred stock and 500,000 shares of our series B-1 preferred stock. We have also paid Archemix an aggregate of $2.0 million in fees based on our achievement of specified clinical milestone events under the C5 License Agreement.

Under the C5 License Agreement, for each anti-C5 aptamer product that we may develop under the agreement, including Zimura, we are obligated to make additional payments to Archemix of up to an aggregate of $57.5 million if we achieve specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $24.5 million of such payments relating to second and third indications and $2.5 million of such payments relating to sustained delivery applications. Under the C5 License Agreement, we are also obligated to make additional payments to Archemix of up to an aggregate of $22.5 million if we achieve specified commercial milestones based on net product sales of all anti-C5 products licensed under the agreement. We are also obligated to pay Archemix a double-digit percentage of specified non-royalty payments we may receive from any sublicensee of our rights under the C5 License Agreement. We are not obligated to pay Archemix a running royalty based on net product sales in connection with the C5 License Agreement.

For more information about the C5 License Agreement, please see the section entitled "Licensing and Other Arrangements—Zimura - Archemix C5 License Agreement" in Part I, Item 1 of this Annual Report on Form 10-K.

Inception 4 Merger Agreement

In October 2018, we and Inception 4 entered into the Inception 4 Merger Agreement, pursuant to which we acquired Inception 4 through a merger transaction. As part of the transaction, we received approximately $6.1 million in cash.

In addition, pursuant to the Inception 4 Merger Agreement, the former equityholders of Inception 4 will be entitled to receive contingent future payments from us based on the achievement of certain clinical and regulatory milestones of up to an aggregate maximum amount of $105 million, with $45 million of such potential payments relating to GA and $60 million of such potential payments relating to wet AMD. These future milestone payments will be payable in the form of shares of our common stock, calculated based on the price of our common stock over a five-trading day period preceding the achievement of the relevant milestone, unless and until the issuance of such shares would, together with all other shares issued in connection with the Inception 4 Merger, exceed an overall maximum limit of approximately 7.2 million shares, which is equal to 19.9% of the number of issued and outstanding shares of our common stock as of the close of business on the business day prior to the closing date of the Inception 4 Merger, and will be payable in cash thereafter.

For more information about the Inception 4 Merger Agreement, please see the section entitled "HtrA1 Inhibitor Program - Inception 4 Merger Agreement" in Part I, Item 1 of this Annual Report on Form 10-K.

RHO-adRP Gene Therapy Agreements with the University of Florida and the University of Pennsylvania

RHO-adRP License Agreement

In June 2018, we paid a $0.5 million upfront license issuance fee to UFRF, on behalf of UFRF and Penn, in connection with entry into the RHO-adRP License Agreement, which was recorded as a research and development expense, as well as accrued patent prosecution expenses of approximately $30 thousand, which was recorded as a general and administrative expense. Under the agreement, we agreed to pay an annual license maintenance fee in the low double-digit thousands of dollars, which will be payable on an annual basis until the first commercial sale of a licensed product. In addition, we agreed to reimburse UFRF for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

We further agreed to pay UFRF, on behalf of both licensors, up to an aggregate of $23.5 million if we achieve specified clinical, marketing approval and reimbursement approval milestones with respect to a licensed product and additionally, up to an aggregate of $70.0 million if we achieve specified commercial sales milestones with respect to a licensed product.

We are also obligated to pay UFRF, on behalf of both licensors, royalties at a low single-digit percentage of net sales of licensed products. Such royalties are subject to customary reductions for lack of patent coverage and loss of regulatory exclusivity. In addition, such royalties with respect to any licensed product in any country may be offset by a specified portion of any royalty payments actually paid by us with respect to such licensed product in such country under third-party licenses for patent rights or other intellectual property rights that are necessary to manufacture, develop and commercialize the licensed product in such country. Our obligation to pay royalties under the RHO-adRP License Agreement will continue on a licensed product-by-licensed product and country-by-country basis until the latest of:

- the expiration of the last-to-expire licensed patent rights covering a licensed product in the country of sale;
- the expiration of regulatory exclusivity covering a licensed product in the country of sale; and
- ten years from the first commercial sale of the applicable licensed product in the country of sale.

Beginning on the earlier of the calendar year following the first commercial sale of a licensed product and the first business day of 2031, we are also obligated to pay certain minimum royalties, not to exceed an amount in the low hundreds of thousands of dollars on an annual basis, which minimum royalties are creditable against our royalty obligation with respect to net sales of licensed products due for the year in which the minimum royalty is paid.

If we or an affiliate sublicenses any of the licensed patent rights to a third party, we will be obligated to pay UFRF, on behalf of both licensors, a low double-digit percentage of the consideration received in exchange for such sublicense, with the applicable percentage based upon the stage of development of the sublicensed product at the time we or the applicable affiliate enters into the sublicense.

If we receive a rare pediatric disease priority review voucher from the FDA in connection with obtaining marketing approval for a licensed product and we subsequently use such priority review voucher in connection with a different product candidate, we will be obligated to pay UFRF, on behalf of both licensors, aggregate payments in the low double-digit millions of dollars based on certain marketing approval and commercial sales milestones with respect to such other product candidate. In addition, if we sell such a priority review voucher to a third party, we will be obligated to pay UFRF, on behalf of both licensors, a low double-digit percentage of any consideration received from such third party in connection with such sale.

For more information about the RHO-adRP License Agreement, please see the section entitled "Licensing and Other Arrangements—RHO-adRP Gene Therapy Product Candidate - RHO-adRP License Agreement" in Part I, Item 1 of this Annual Report on Form 10-K.

RHO-adRP Master Sponsored Research Agreement

In June 2018, we also entered into a Master Sponsored Research Agreement, or the Master SRA, with Penn. Under the Master SRA, Penn has agreed to perform, on a project basis, certain sponsored research and to provide the results of such research to us. The scope of each project and certain associated terms, including financial terms, are to be specified in a statement of work for each project.

Under the Master SRA, Penn has granted us an exclusive first option to obtain, for no additional consideration and pursuant to the terms of the RHO-adRP License Agreement, an exclusive license to any patents or patent applications resulting from the sponsored research that is fully-funded by us and that relate to the patent rights licensed under the RHO-adRP License Agreement. In addition, under the Master SRA, Penn has granted us an exclusive first option to negotiate to acquire an exclusive license, on commercially reasonable terms, to any patents or patent applications resulting from the sponsored research that do not relate to the patent rights licensed under the RHO-adRP License Agreement.

The initial term of the Master SRA expires on June 6, 2021, provided that in the event of a termination of the Master SRA, any statements of work in effect at the time of such termination shall continue in effect, subject to the terms of the Master

SRA, until expiration or termination of the applicable statement of work. Either party may terminate the Master SRA or a statement of work if the other party breaches any of the terms or conditions of the Master SRA or statement of work, as applicable, and does not cure such breach within a specified cure period. In addition, either party may terminate an applicable statement of work if the services of the applicable principal investigator are no longer available to Penn and an acceptable substitute is not appointed within an agreed-upon period. The Master SRA contains indemnification and dispute resolution provisions that are customary for agreements of its kind.

We and Penn have entered into a series of statements of work under the Master SRA pursuant to which Penn is conducting additional preclinical studies for our RHO-adRP gene therapy product candidate, as well as a natural history study of RHO-adRP patients. The total amount of funding for the sponsored research covered by these statements of work that we have committed to date and are expecting to commit to is in the low single-digit millions of dollars.

Prior Licensing and Commercialization Agreement with Novartis Pharma AG

In May 2014, we entered into the Novartis Agreement with Novartis. Under the Novartis Agreement, we granted Novartis exclusive rights under specified patent rights, know-how and trademarks controlled by us to manufacture standalone Fovista products and products combining Fovista with an anti-VEGF agent to which Novartis has rights in a co-formulated product, for the treatment, prevention, cure or control of any human disease, disorder or condition of the eye, and to develop and commercialize those licensed products in all countries outside of the United States, which we refer to as the Novartis Territory.

In July 2017, we and Novartis entered into the July 2017 Letter Agreement to streamline the process and timeline for evaluating data from the OPH1004 trial once it became available. The July 2017 Letter Agreement provides Novartis with a fully paid-up, royalty-free license to use data from the Lucentis monotherapy arms of our Phase 2b OPH1001 trial and Phase 3 OPH1002 and OPH1003 trials in the Novartis Territory in connection with the development, manufacturing and commercialization of Novartis-controlled anti-VEGF products. The Lucentis study data license will continue until July 3, 2022. In October 2017, following the failure of the Phase 3 Fovista program and pursuant to the terms of the July 2017 Letter Agreement, Novartis elected to terminate the Novartis Agreement with immediate effect.

Novartis paid us a $200.0 million upfront fee upon execution of the Novartis Agreement. Novartis also paid us $50.0 million upon the achievement of each of two patient enrollment-based milestones, and $30.0 million upon the achievement of a third, and final, enrollment-based milestone, for an aggregate of $130.0 million in milestone payments.

Prior Royalty Financing Agreement with Novo Holdings A/S

In May 2013, we entered into the Novo Agreement, pursuant to which we obtained financing in three tranches in an aggregate amount equal to $125.0 million in return for the sale to Novo of aggregate royalties of a mid-single-digit percentage on worldwide sales of Fovista, certain Fovista-related products, or Fovista-Related Products, and certain other antagonists of PDGF. We refer to these collective products as the Anti-PDGF Royalty Products. The three tranches of financing, in which Novo purchased three low single-digit royalty interests and paid us $125.0 million in the aggregate, closed in May 2013, January 2014 and November 2014.

We used a portion of the proceeds that we initially received under the Novo Agreement to repay in full an aggregate of $14.4 million of outstanding principal, interest and fees under our venture debt facility and used the remaining proceeds to support clinical development and regulatory activities for Fovista and for general corporate expenses.

On December 31, 2018, we and Novo entered into the Novo Termination Agreement, that terminated the Novo Agreement. As a result of the Novo Termination Agreement, Novo relinquished all rights to receive royalties based on net sales of Anti-PDGF Royalty Products. In exchange, we agreed to forbear from any future filing, prosecution, maintenance or enforcement of any intellectual property rights related to Anti-PDGF Royalty Products, and from granting any third party or affiliate any right or license in any such intellectual property rights or clinical study data generated by or on behalf of us, our affiliates or licensees or sublicensees, for the development, manufacture or commercialization of Anti-PDGF Royalty Products or any other antagonists of PDGF. The foregoing restriction does not apply to gene therapies (so long as we do not grant any rights or licenses to intellectual property or clinical study data related to Fovista or Fovista-Related Products). We further agreed, until December 31, 2028, not to develop, manufacture, seek or obtain regulatory approval for or commercialize any Anti-PDGF Royalty Products without the prior written consent of Novo. The foregoing restriction does not apply to any gene therapies (so long as we do not utilize data related to Fovista or Fovista-Related Products).

As a result of the Novo Termination Agreement, we extinguished the $125.0 million royalty purchase liability from our Consolidated Balance Sheet as of December 31, 2018 and recognized a related gain of $125.0 million in our Consolidated Statements of Operations for the year ended December 31, 2018. The extinguishment of the royalty purchase liability and the

related gain did not impact our cash balance during this period as we had received the proceeds related to the royalty purchase liability in prior periods.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2018:

	Payments Due by Period				
	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
	(in thousands)				
Sponsored Research (1)	$ 3,060	$ 2,658	$ 402	$ —	$ —
Operating Leases (2)	1,544	1,040	504	—	—
Total (3)	$ 4,604	$ 3,698	$ 906	$ —	$ —

(1) The table above includes our contracted obligations under our sponsored research agreements. We have engaged academic research collaborators to conduct research that has the potential to create or enhance technologies to which we may acquire or in-license rights to for development of new products or product candidates.

(2) The table above includes our continuing rent obligations through June 2020. In June 2018, we and One Penn Plaza LLC entered into an amendment to the lease for office space at One Penn Plaza in New York, New York extending the term of our lease, which was scheduled to expire in December 2018, through the end of June 2020.

(3) This table does not include:

- any milestone payments which may become payable to third parties under license or acquisition agreements as the timing and likelihood of such payments are not known with certainty;
- any royalty payments to third parties as the amounts, timing and likelihood of such payments are not known;
- anticipated expenditures under supply agreements for periods for which we are not yet bound under binding purchase orders;
- contracts that are entered into in the ordinary course of business that are not material in the aggregate in any period presented above; or
- our royalty purchase liability of $125.0 million, which was extinguished as of December 31, 2018.

In addition to the amounts set forth in the table above, we may be required, under the C5 License Agreement, the Inception 4 Merger Agreement or the RHO-adRP License Agreement to make milestone payments and/or pay royalties as described above.

We also have letter agreements with certain employees that require the funding of a specific level of payments, if certain events, such as a termination of employment in connection with a change in control or termination of employment by the employee for good reason or by us without cause, occur. For a description of these obligations, see our definitive proxy statement on Schedule 14A for our 2018 annual meeting of stockholders, as filed with the SEC on April 17, 2018.

In addition, in the course of normal business operations, we have agreements with contract service providers to assist in the performance of our research and development and manufacturing activities. Expenditures to CROs and CMOs represent significant costs in preclinical and clinical development. Subject to required notice periods and our obligations under binding purchase orders and any cancellation fees that we may be obligated to pay, we can elect to discontinue the work under these agreements at any time. We may also enter into additional collaborative research, contract research, manufacturing, and supplier agreements in the future, which may require upfront payments and even long-term commitments of cash.

Off-Balance Sheet Arrangements

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

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risk related to changes in interest rates. We had cash and cash equivalents of $131.2 million as of December 31, 2018, consisting of cash and investments in money market funds and certain short-term investment-grade corporate debt securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because a significant portion of our investments are in short-term securities. Due to the low risk profile of our investments, an immediate 100 basis point change in interest rates would not have a material effect on the fair market value of our portfolio.

We contract with CROs globally. We may be subject to fluctuations in foreign currency rates in connection with certain of these agreements. Transactions denominated in currencies other than the U.S. dollar are recorded based on exchange rates at the time such transactions arise. As of December 31, 2018, substantially all of our total liabilities were denominated in the U.S. dollar.

Item 8. Financial Statements and Supplementary Data

Our financial statements, together with the report of our independent registered public accounting firm, appear on pages F-2 through F-31 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Based on the evaluation of our disclosure controls and procedures as of December 31, 2018, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed by, or under the supervision of our Chief Executive Officer and our Chief Financial Officer, and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in the original *Internal Control—Integrated Framework* updated in 2013. Based on that assessment, our management concluded that, as of December 31, 2018, our internal control over financial reporting was effective.

The effectiveness of the Company's internal control over financial reporting as of December 31, 2018, has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which appears herein.

Changes in Internal Control Over Financial Reporting

No changes in our internal control over financial reporting (as defined in Rules 13a-15(d) and 15d-15(d) under the Exchange Act) occurred during the quarter ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Ophthotech Corporation

Opinion on Internal Control over Financial Reporting

We have audited Ophthotech Corporation's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Ophthotech Corporation (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on the COSO criteria**.**

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2017, and the consolidated statements of operations, comprehensive income (loss), stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2018 and the related notes and our report dated February 28, 2019 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Iselin, New Jersey

February 28, 2019

Item 9B. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Directors and Executive Officers

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Compliance with Section 16(a) of the Exchange Act

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Code of Ethics

We have adopted a code of business conduct and ethics that applies to our directors and officers (including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions) as well as our other employees. A copy of our code of business conduct and ethics is available on our website. We intend to post on our website all disclosures that are required by applicable law, the rules of the SEC or the Nasdaq Global Market concerning any amendment to, or waiver of, our code of business conduct and ethics.

Director Nominees

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Audit Committee

We have separately designated a standing Audit Committee established in accordance with Section 3(a)(58)(A) of the Exchange Act. Additional information regarding the Audit Committee that is required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Audit Committee Financial Expert

Our board of directors has determined that Jane Henderson is an "audit committee financial expert" as defined by Item 407(d)(5) of Regulation S-K of the Exchange Act and Ms. Henderson and the other members of our Audit Committee are "independent" under the rules of the Nasdaq Global Market.

Item 11. Executive Compensation

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Item 14. Principal Accountant Fees and Services

The information required by this item will be set forth in our Proxy Statement for the 2019 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(1) Financial Statements

The following financial statements are filed as part of this Annual Report on Form 10-K:

	Page
Report of Independent Registered Public Accounting Firm	F-2
Consolidated Balance Sheets as of December 31, 2018 and 2017	F-3
Consolidated Statements of Operations for the Years Ended December 31, 2018, 2017 and 2016	F-4
Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2018, 2017 and 2016	F-5
Consolidated Statements of Changes in Stockholders' Equity (Deficit) for the Years Ended December 31, 2018, 2017 and 2016	F-6
Consolidated Statements of Cash Flows for the Years Ended December 31, 2018, 2017 and 2016	F-7
Notes to Consolidated Financial Statements	F-8

(2) Financial Statement Schedules

No financial statement schedules have been filed as part of this Annual Report on Form 10-K because they are not applicable, not required or because the information is otherwise included in our financial statements or notes thereto.

(3) Exhibits

Exhibit Number		Description of Exhibit
2.1	† *	Agreement and Plan of Merger, dated October 30, 2018, by and among the Registrant, Orion Ophthalmology Merger Sub Inc., Orion Ophthalmology LLC, Inception 4, Inc., and solely in its capacity as equityholder representative, Fortis Advisors LLC (incorporated by reference to Exhibit 2.1 of the Registrant's Current Report on Form 8-K filed on October 31, 2018)
3.1		Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.3 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
3.2		Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.4 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
4.1		Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
10.1	+	Amended and Restated 2007 Stock Incentive Plan, as amended (incorporated by reference to Exhibit 10.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-190643))
10.2	+	Form of Incentive Stock Option Agreement under Amended and Restated 2007 Stock Incentive Plan (incorporated by reference to Exhibit 10.2 of the Registrant's Registration Statement on Form S-1 (File No. 333-190643))
10.3	+	Form of Nonstatutory Stock Option Agreement under Amended and Restated 2007 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 of the Registrant's Registration Statement on Form S-1 (File No. 333-190643))
10.4	+	2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 of the Registrant's Annual Report on Form 10-K filed on March 2, 2015)
10.5	+	Amendment No. 1 to Stock Incentive Plan, adopted June 4, 2015 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 10, 2015)
10.6	+	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
10.7	+	Form of Nonqualified Stock Option Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.6 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
10.8	+	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (incorporated by reference to Exhibit 10.7 of the Registrant's Annual Report on Form 10-K filed on March 2, 2015)

10.9	+	2016 Employee Stock Purchase Plan (incorporated by reference to Exhibit 99.1 of the Registrant's Registration Statement on Form S-8 (File No. 333-211916))
10.10		Lease Agreement, dated as of September 30, 2007, between the Registrant and One Penn Plaza LLC, as the same has been supplemented by agreement dated March 12, 2013 and amended by the Amendment of Lease, dated as of August 30, 2013, Second Amendment to Lease, entered into on January 7, 2014, Third Amendment of Lease, dated as of April 18, 2014, the Fourth Amendment of Lease, dated as of December 22, 2014, and the Fifth Amendment of Lease, dated as of October 1, 2017 (incorporated by reference to Exhibit 10.11 of the Registrant's Annual Report on Form 10-K filed on March 5, 2018)
10.11		Sixth Amendment of Lease, dated as of June 29, 2018, between the Registrant and One Penn Plaza LLC (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2018)
10.12	†	Amended and Restated Exclusive License Agreement, dated as of September 12, 2011, by and between the Registrant and Archemix Corp., as amended by Amendment No. 1 thereto dated December 20, 2011 and supplemented by a letter agreement, dated as of April 30, 2012 (incorporated by reference to Exhibit 10.11 of the Registrant's Registration Statement on Form S-1 (File No. 333-190643))
10.13	†	Exclusive License Agreement with Know-How by and among The University of Florida Research Foundation, Incorporated, The Trustees of the University of Pennsylvania and the Registrant dated June 6, 2018 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2018)
10.14	†	Master Sponsored Research Agreement by and between The Trustees of the University of Pennsylvania and the Registrant dated June 6, 2018 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2018)
10.15	†	Clinical and Commercial Services Agreement Between the Registrant and Ajinomoto Althea, Inc., dated October 31, 2016 (incorporated by reference to Exhibit 10.38 of the Registrant's Annual Report on Form 10-K filed on February 28, 2017)
10.16		Stockholder Agreement, dated October 30, 2018, by and among the Registrant, Versant Venture Capital IV, L.P., Versant Side Fund IV, L.P. and Versant Venture Management LLC (incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on October 31, 2018)
10.17	+	Offer of Employment between the Registrant and David Guyer (incorporated by reference to Exhibit 10.14 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
10.18	+	Letter Agreement between the Registrant and David R. Guyer dated February 26, 2015, amending the Offer of Employment between the Registrant and David R. Guyer dated April 26, 2013 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on May 11, 2015)
10.19	+	Letter Agreement between the Registrant and David R. Guyer, dated April 24, 2017 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 2, 2017)
10.20	+	Letter agreement by and between the Registrant and David R. Guyer dated May 11, 2018 (incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2018)
10.21	+	Letter agreement by and between the Registrant and David R. Guyer dated May 24, 2018 (incorporated by reference to Exhibit 10.5 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2018)
10.22	+	Letter Agreement between the Registrant and Glenn P. Sblendorio, dated January 4, 2016 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2016)
10.23	+	Letter Agreement between the Registrant and Glenn P. Sblendorio, dated January 4, 2016 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2016)
10.24	+	Letter Agreement between the Registrant and Glenn P. Sblendorio, dated April 24, 2017 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on August 2, 2017)
10.25	+	Letter Agreement between the Registrant and David F. Carroll, dated April 25, 2017 (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on August 2, 2017)
10.26	+	Promotion Letter between the Registrant and Keith Westby, dated January 30, 2017 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on May 3, 2017)
10.27	+	Letter Agreement between the Registrant and Keith Westby, dated February 2, 2017 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on May 3, 2017)
10.28	+	Form of Indemnification Agreement between the Registrant and each Director and Executive Officer (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on August 5, 2016)
10.29		Sales Agreement by and between Cowen and Company, LLC and the Registrant dated August 1, 2018 (incorporated by reference to Exhibit 1.2 of the Registrant's Registration Statement on Form S-3 filed on August 1, 2018)
21.1		List of Subsidiaries

23.1	Consent of Ernst & Young LLP
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended
32.1	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
32.2	Certification of principal financial officer pursuant to 18 U.S.C. §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 Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Label Linkbase Document
101.PRE	XBRL Taxonomy Presentation Linkbase Document

† Confidential treatment has been granted as to certain portions, which portions have been omitted and separately filed with the Securities and Exchange Commission.

+ Management contract or compensatory plan or arrangement filed in response to Item 15(a)(3) of the Instructions to the Annual Report on Form 10-K.

* Schedules have been omitted from this exhibit pursuant to Item 601(b)(2) of Regulation S-K. A copy of any omitted schedule will be furnished supplementally to the Securities and Exchange Commission upon request; provided, however, that the registrant may request confidential treatment for any document so furnished.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: February 28, 2019

OPHTHOTECH CORPORATION

By: /s/ GLENN P. SBLENDORIO

Glenn P. Sblendorio
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ GLENN P. SBLENDORIO Glenn P. Sblendorio	President, Chief Executive Officer and Director (principal executive officer)	February 28, 2019
/s/ DAVID F. CARROLL David F. Carroll	Senior Vice President and Chief Financial Officer (principal financial and accounting officer)	February 28, 2019
/s/ AXEL BOLTE Axel Bolte	Director	February 28, 2019
/s/ THOMAS DYRBERG Thomas Dyrberg, M.D., D.M.Sc.	Director	February 28, 2019
/s/ ADRIENNE L. GRAVES, Ph.D. Adrienne L. Graves, Ph.D.	Director	February 28, 2019
/s/ DAVID R. GUYER David R. Guyer, M.D.	Executive Chairman of the Board of Directors	February 28, 2019
/s/ JANE P. HENDERSON Jane P. Henderson	Director	February 28, 2019
/s/ DAVID E. REDLICK David E. Redlick	Director	February 28, 2019
/s/ CALVIN W. ROBERTS, M.D. Calvin W. Roberts, M.D.	Director	February 28, 2019

OPHTHOTECH CORPORATION

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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Ophthotech Corporation

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ophthotech Corporation (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive income (loss), stockholders' equity (deficit) and cash flows for each of the three 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 three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 28, 2019 expressed an unqualified opinion thereon.

Basis for Opinion

These consolidated 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 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. 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 2008.

Iselin, New Jersey
February 28, 2019

Ophthotech Corporation

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2018	December 31, 2017
Assets		
Current assets		
Cash and cash equivalents	$ 131,201	$ 166,972
Prepaid expenses and other current assets	2,086	3,146
Income tax receivable	—	1,387
Total current assets	133,287	171,505
Property and equipment, net	335	518
Income tax receivable, non-current	3,529	—
Deferred tax assets	—	3,529
Other assets	14	24
Total assets	$ 137,165	$ 175,576
Liabilities and Stockholders' Equity		
Current liabilities		
Accrued research and development expenses	$ 7,337	$ 4,984
Accounts payable and accrued expenses	5,869	7,551
Total current liabilities	13,206	12,535
Royalty purchase liability	—	125,000
Total liabilities	13,206	137,535
Stockholders' equity		
Preferred stock—$0.001 par value, 5,000,000 shares authorized, no shares issued or outstanding	$ —	$ —
Common stock—$0.001 par value, 200,000,000 shares authorized, 41,397,197 and 36,110,298 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	41	36
Additional paid-in capital	545,585	522,759
Accumulated deficit	(421,667)	(484,754)
Total stockholders' equity	123,959	38,041
Total liabilities and stockholders' equity	$ 137,165	$ 175,576

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

Ophthotech Corporation

Consolidated Statements of Operations

(in thousands, except per share data)

	Years ended December 31,		
	2018	2017	2016
Collaboration revenue	$ —	$ 209,977	$ 50,909
Operating expenses:			
Research and development	41,737	66,289	196,295
General and administrative	23,612	35,683	50,178
Total operating expenses	65,349	101,972	246,473
Income (loss) from operations	(65,349)	108,005	(195,564)
Interest income	2,389	1,522	1,704
Gain on extinguishment of Royalty Purchase Liability	125,000	—	—
Other income (expense)	(16)	(34)	34
Income (loss) before income tax benefit	62,024	109,493	(193,826)
Income tax benefit	(1,063)	(4,712)	(406)
Net income (loss)	$ 63,087	$ 114,205	$ (193,420)
Net income (loss) per common share:			
Basic	$ 1.70	$ 3.18	$ (5.45)
Dilutive	1.70	3.17	(5.45)
Weighted average common shares outstanding:			
Basic	37,061	35,919	35,486
Dilutive	37,088	36,007	35,486

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

Ophthotech Corporation

Consolidated Statements of Comprehensive Income (Loss)

(in thousands)

	Years ended December 31,		
	2018	**2017**	**2016**
Net Income (loss)	$ 63,087	$ 114,205	$ (193,420)
Other comprehensive income			
Unrealized gain on available for sale securities, net of tax	—	212	261
Other comprehensive income	—	212	261
Comprehensive income (loss)	$ 63,087	$ 114,417	$ (193,159)

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

Ophthotech Corporation

Consolidated Statements of Stockholders' Equity (Deficit)

(in thousands)

	Junior Series A Preferred Stock		Common Stock		Additional paid-in capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total
	Shares	Amount	Shares	Amount				
Balance at December 31, 2015	—	$ —	35,197	$ 35	$ 465,924	$ (405,539)	$ (473)	$ 59,947
Issuance of common stock under employee stock compensation plans and warrants	—	—	536	1	6,933	—	—	6,934
Share-based compensation	—	—	—	—	—	—	—	—
Excess tax benefit from share-based compensation	—	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	(193,420)	—	(193,420)
Unrealized loss on available for sale securities, net of tax	—	—	—	—	—	—	261	261
Balance at December 31, 2016	—	$ —	35,733	$ 36	$ 504,517	$ (598,959)	$ (212)	$ (94,618)
Issuance of common stock under employee stock compensation plans and warrants	—	—	377	—	71	—	—	71
Share-based compensation	—	—	—	—	18,171	—	—	18,171
Net income					—	114,205	—	114,205
Unrealized gain on available for sale securities, net of tax	—	—	—	—	—	—	212	212
Balance at December 31, 2017	—	$ —	36,110	$ 36	$ 522,759	$ (484,754)	$ —	$ 38,041
Issuance of common stock related to acquisition	—	—	5,175	5	11,689	—	—	11,694
Issuance of common stock under employee stock compensation plans	—	—	112	—	65	—	—	65
Share-based compensation	—	—	—	—	11,072	—	—	11,072
Net income	—	—	—	—	—	63,087	—	63,087
Unrealized gain on available for sale securities, net of tax	—	—	—	—	—	—	—	—
Balance at December 31, 2018	—	$ —	41,397	$ 41	$ 545,585	$ (421,667)	$ —	$ 123,959

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

Ophthotech Corporation

Consolidated Statements of Cash Flows

(in thousands)

	Years ended December 31,		
	2018	2017	2016
Operating Activities			
Net income (loss)	$ 63,087	$ 114,205	$ (193,420)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities			
Depreciation	183	2,763	757
Amortization of premium and discounts on investment securities	—	140	595
Non-cash charge on acquired in-process research and development	5,619	—	—
Non-cash gain on extinguishment of royalty purchase agreement	(125,000)	—	—
Deferred income taxes	—	(3,366)	22,954
Share-based compensation	11,072	18,171	31,660
Changes in operating assets and liabilities:			
Income tax receivable	1,387	(1,387)	3,421
Due from Novartis Pharma AG	—	3,531	858
Prepaid expense and other current assets	1,060	(68)	(995)
Accrued interest receivable	—	466	203
Other assets	10	438	27
Accrued research and development expenses	2,353	(42,256)	28,420
Accounts payable and accrued expenses	(1,682)	(4,481)	14
Deferred revenue	—	(209,977)	(3,090)
Net cash used in operating activities	(41,911)	(121,821)	(108,596)
Investing Activities			
Purchase of marketable securities	—	(12,014)	(72,197)
Maturities of marketable securities	—	166,806	86,500
Purchase of property and equipment	—	—	(572)
Net cash provided by investing activities	—	154,792	13,731
Financing Activities			
Proceeds from issuance of common stock related to acquisition	6,075	—	—
Proceeds from employee stock plan purchases and stock option exercises	65	71	6,934
Net cash provided by financing activities	6,140	71	6,934
Net change in cash and cash equivalents	(35,771)	33,042	(87,931)
Cash and cash equivalents			
Beginning of period	166,972	133,930	221,861
End of period	$ 131,201	$ 166,972	$ 133,930
Supplemental disclosure of cash paid			
Income taxes received, net	$ (2,467)	$ (245)	$ (26,998)
Supplemental disclosures of non-cash information related to investing activities			
Change in unrealized gain (loss) on available for sale securities, net of tax	$ —	$ 212	$ 261
Common stock issued to acquire net assets of Inception 4, Inc.	$ 11,694	$ —	$ —

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

Ophthotech Corporation

Notes to Consolidated Financial Statements

(tabular dollars and shares in thousands, except per share data)

1. Business

Description of Business and Organization

Ophthotech Corporation (the “Company” or “Ophthotech”) was incorporated on January 5, 2007, in Delaware. The Company is a science-driven biopharmaceutical company specializing in the development of novel therapies to treat ophthalmic diseases, with a focus on age-related and orphan retinal diseases. The Company is seeking to leverage its development platform, clinical experience and retina expertise to develop both therapeutics and gene therapies in these disease areas.

The Company currently has ongoing research and development programs for both therapeutics and gene therapy product candidates and technologies.

The Company's therapeutics portfolio consists of Zimura® (avacincaptad pegol), which is a C5 complement inhibitor, and its program of High temperature requirement A serine peptidase 1 protein ("HtrA1") inhibitors. The Company has Phase 2b clinical trials ongoing evaluating Zimura for the treatment of:

- geographic atrophy ("GA"), which is a late-stage form of dry age-related macular degeneration ("AMD") characterized by retinal cell death and degeneration of tissue in the central portion of the retina, referred to as the macula, and which may result in loss of vision; and
- autosomal recessive Stargardt disease, which is an orphan inherited retinal disease ("IRD") that also may result in loss of vision.

The Company previously also evaluated Zimura in combination with Lucentis® (ranibizumab), an anti-vascular endothelial growth factor ("anti-VEGF") agent, for the treatment of wet AMD, for which it completed a Phase 2a clinical trial during the fourth quarter of 2018. The Company does not currently have plans to develop Zimura further in wet AMD. The Company's HtrA1 inhibitor program, which it is developing for GA secondary to dry AMD and potentially other retinal diseases such as wet AMD and idiopathic polypoidal choroidal vasculopathy, is in the preclinical stage of development.

The Company's gene therapy portfolio consists of several ongoing research and preclinical development programs that use adeno-associated virus ("AAV") for gene delivery. These AAV gene therapy programs are targeting the following orphan IRDs:

- rhodopsin-mediated autosomal dominant retinitis pigmentosa ("RHO-adRP") which is characterized by progressive and severe bilateral loss of vision leading to blindness;
- Best vitelliform macular dystrophy which is characterized by bilateral egg yolk-like macular lesions that, over time, progress to atrophy and loss of vision, and potentially other diseases associated with mutations in the *Best1* gene, which is referred to as bestrophinopathies;
- Leber Congenital Amaurosis type 10, which is characterized by severe bilateral loss of vision at or soon after birth; and
- autosomal recessive Stargardt disease.

The Company's business development efforts in 2018 have resulted in the expansion of its research and development pipeline, with the initiation of the Company's gene therapy sponsored research programs with the University of Massachusetts Medical School ("UMMS") in February 2018, the in-license of the Company's RHO-adRP gene therapy product candidate in June 2018 from the University of Florida Research Foundation ("UFRF") and the University of Pennsylvania ("Penn"), the acquisition of its HtrA1 inhibitor program through the acquisition of Inception 4, Inc. ("Inception 4") in October 2018 (See Note 5—Inception 4 Acquisition for a description of this acquisition) and the entry into its exclusive option agreement with Penn and UFRF for gene therapy product candidates for bestrophinopathies in October 2018.

2. Summary of Significant Accounting Policies

Basis of Presentation and Consolidation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include all adjustments necessary for the fair presentation of the Company's financial position for the periods presented. The consolidated financial statements include the accounts of Ophthotech and its subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Segment and geographic information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating and reporting segment.

Use of Estimates

The preparation of financial statements and related disclosures in conformity with GAAP requires management to make estimates and judgments that affect the amounts reported in the financial statements and accompanying notes. The Company bases its estimates and judgments on historical experience and on various other assumptions that it believes are reasonable under the circumstances. The amounts of assets and liabilities reported in the Company's Consolidated Balance Sheets and the amount of expenses reported for each of the periods presented are affected by estimates and assumptions, which are used for, but not limited to, accounting for research and development costs, revenue recognition, accounting for share-based compensation and accounting for income taxes. Actual results could differ from those estimates.

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of 90 days or less when purchased to be cash equivalents. The carrying amounts reported in the Balance Sheets for cash and cash equivalents are valued at cost, which approximates their fair value.

As of December 31, 2018, the Company had cash and cash equivalents of approximately $131.2 million. The Company believes that its existing cash and cash equivalents as of December 31, 2018 will be sufficient to fund its operations and capital expenditure requirements as currently planned for at least the next 12 months.

Revenue Recognition

Collaboration Revenue

Prior to 2018, the Company's revenue resulted from payments received under its May 2014 licensing and commercialization agreement (the “Novartis Agreement”) with Novartis Pharma AG ("Novartis"), as modified by the July 2017 letter agreement entered into by the Company and Novartis in relation to the Novartis Agreement (the "July 2017 Letter Agreement"). See "Note 6—Licensing and Commercialization Agreements" below for a description of these agreements. The Company used the relative selling price method to allocate arrangement consideration to the Company’s performance obligations under the Novartis Agreement. The Company completed the deliverables under the Novartis Agreement and the July 2017 Letter Agreement during the third quarter of 2017.

As the Company has no products approved for sale, the Company does not expect to receive any revenue from product candidates that it develops until it potentially obtains regulatory approval and commercializes such products, or until the Company potentially enters into agreements with third parties for the development and commercialization of its product candidates. If the Company's development efforts for any of its product candidates result in regulatory approval or the Company enters into collaboration agreements with third parties, the Company may generate revenue from product sales or from such third parties.

In the future, the Company will evaluate revenue contracts and arrangements, if any, following the provisions of the Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC"), *Revenue from Contracts with Customers (Topic 606).*

2. Summary of Significant Accounting Policies (Continued)

Business combinations and asset acquisitions

The Company evaluates acquisitions of assets and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen (as adopted in the current period under Accounting Standards Update (ASU) No. 2017-01, "Business Combinations (Topic 805): Clarifying the Definition of a Business"—see "Recently Adopted Accounting Standards" for further details) to determine if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If the screen is met, the transaction is accounted for as an asset acquisition. If the screen is not met, further determination is required as to whether or not the Company has acquired inputs and processes that have the ability to create outputs, which would meet the requirements of a business. If determined to be a business combination, the Company records all assets and liabilities of the acquired business, including goodwill and other identified intangible assets, at their respective fair values as of the acquisition date. Contingent consideration, if any, is recognized at its fair value on the acquisition date and changes in fair value are recognized in earnings until settlement. Acquisition-related transaction costs are expensed as incurred.

If determined to be an asset acquisition, the Company accounts for the transaction under ASC 805-50, which requires the acquiring entity in an asset acquisition to recognize assets (net assets) based on the cost to the acquiring entity on a relative fair value basis, which includes transaction costs in addition to consideration given. No gain or loss is recognized as of the date of acquisition unless the fair value of noncash assets given as consideration differs from the assets' carrying amounts on the acquiring entity's books. Consideration transferred that is noncash will be measured based on either the cost (which shall be measured based on the fair value of the consideration given) or the fair value of the assets (net assets) acquired, whichever is more reliably measurable. Goodwill is not recognized in an asset acquisition and any excess consideration transferred over the fair value of the net assets acquired is allocated to the identifiable assets based on relative fair values. In-process research and development acquired in connection with an asset acquisition is expensed in accordance with FASB ASC 730, *Research and Development,* when there is no alternative future use.

Contingent consideration payments in asset acquisitions are recognized when the contingency is resolved and the consideration is paid or becomes payable (unless the contingent consideration meets the definition of a derivative, in which case the amount becomes part of the basis in the asset acquired). Upon recognition of the contingent consideration payment, the amount is included in the cost of the acquired asset or group of assets.

Concentration of Credit Risk

The Company's financial instruments that are exposed to concentration of credit risk consist primarily of cash and cash equivalents. The Company maintains its cash in bank accounts, which generally exceed federally insured limits. The Company maintains its cash equivalents in investments in money market funds and, at times, in U.S. Treasury securities and investment-grade corporate debt securities with original maturities of 90 days or less.

The Company believes it is not exposed to significant credit risk on its cash and cash equivalents.

Concentration of Suppliers

The Company currently relies exclusively upon a single third-party manufacturer to provide supplies of the active pharmaceutical ingredient ("API") for Zimura on a purchase order basis. The Company also engages a single third-party manufacturer to provide fill/finish services for clinical supplies of Zimura. In addition, the Company currently relies upon a single third-party supplier to supply it with the proprietary polyethylene glycol reagent used to manufacture Zimura on a purchase order basis. Furthermore, the Company and its contract manufacturers currently rely upon sole-source suppliers of certain raw materials and other specialized components of production used in the manufacture and fill/finish of Zimura. The Company has engaged a single third-party contract manufacturer for its RHO-adRP gene therapy product candidate and expects to rely on sole-source suppliers for certain starting materials to be used in the manufacture of such product candidate. The Company has recently engaged a single third-party contract manufacturer for the BEST1 gene therapy product candidate for which it is planning to commence IND-enabling studies and expects to rely on sole-source suppliers for certain starting materials to be used in the manufacture of such product candidate. If the Company’s third-party manufacturers, fill/finish service providers or starting material suppliers should become unavailable to the Company for any reason, including as a result of capacity constraints, financial difficulties or insolvency, the Company believes that there are a limited number of potential

2. Summary of Significant Accounting Policies (Continued)

replacement manufacturers or suppliers, and the Company likely would incur added costs and delays in identifying or qualifying such replacements.

Foreign Currency Translation

The Company considers the U.S. dollar to be its functional currency. Expenses denominated in foreign currencies are translated at the exchange rate on the date the expense is incurred. The effect of exchange rate fluctuations on translating foreign currency assets and liabilities into U.S. dollars is included in the Statements of Operations. Foreign exchange transaction gains and losses are included in the results of operations and are not material in the Company's financial statements.

Financial Instruments

Cash equivalents are reflected in the accompanying financial statements at fair value. The carrying amount of accounts payable and accrued expenses, including accrued research and development expenses, approximates fair value due to the short-term nature of those instruments.

ASC 820, *Fair Value Measurements and Disclosures*, defines fair value as the price that would be received to sell an asset, or paid to transfer a liability, in the principal or most advantageous market in an orderly transaction between market participants on the measurement date. The fair value standard also establishes a three-level hierarchy, which requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value.

The Company reviews investments on a periodic basis for other than temporary impairments. This review is subjective as it requires management to evaluate whether an event or change in circumstances has occurred in the period that may have a significant adverse effect on the fair value of the investment. The Company uses the market approach to measure fair value for its financial assets. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets. The Company classifies its corporate debt securities within the fair value hierarchy as Level 2 assets, as it primarily utilizes quoted market prices or rates for similar instruments to value these securities.

The valuation hierarchy is based upon the transparency of inputs to the valuation of an asset or liability on the measurement date. The three levels are defined as follows:

- Level 1—inputs to the valuation methodology are quoted prices (unadjusted) for an identical asset or liability in an active market. The Company's Level 1 assets consist of investments in money market funds and U.S. Treasury securities.
- Level 2—inputs to the valuation methodology include quoted prices for a similar asset or liability in an active market or model-derived valuations in which all significant inputs are observable for substantially the full term of the asset or liability. The Company's Level 2 assets consist of investments in investment-grade corporate debt securities.
- Level 3—inputs to the valuation methodology are unobservable and significant to the fair value measurement of the asset or liability. The Company does not hold any assets that are measured using Level 3 inputs.

Property and Equipment

Property and equipment, which consists mainly of manufacturing and clinical equipment, furniture and fixtures, computers, software, and other office equipment, and leasehold improvements, are carried at cost less accumulated depreciation. Depreciation is computed over the estimated useful lives of the respective assets, generally three to ten years, using the straight-line method. Amortization of leasehold improvements is recorded over the shorter of the lease term or estimated useful life of the related asset.

Research and Development

Research and development expenses primarily consist of costs associated with the manufacturing, development and clinical testing of Zimura and, historically, Fovista, as well as costs associated with the preclinical development of other product candidates, formulations and technologies, including costs associated with its HtrA1 inhibitor program, costs associated with its RHO-adRP gene therapy product candidate, including related sponsored research with Penn, costs associated with the BEST1 gene therapy product candidate for which the Company is planning to commence IND-enabling studies, and costs associated with its ongoing gene therapy sponsored research programs with UMMS. Research and development expenses consist of:

2. Summary of Significant Accounting Policies (Continued)

- external research and development expenses incurred under arrangements with third parties, such as academic research collaborators, contract research organizations ("CROs") and other vendors and contract manufacturing organizations ("CMOs") for the production of drug substance and drug product; and
- employee-related expenses for employees dedicated to research and development activities, including salaries, benefits and share-based compensation expense.

Research and development expenses also include costs of acquired product licenses, in-process research and development, and related technology rights where there is no alternative future use, costs of prototypes used in research and development, consultant fees and amounts paid to collaborative partners.

The Company expects its research and development expenses to increase as the Company pursues the development of Zimura, its HtrA1 inhibitor program, its RHO-adRP gene therapy product candidate and the BEST1 gene therapy product candidates for which it holds an option from Penn and UFRF. The Company also expects to incur research and development expenses in connection with its collaborative gene therapy sponsored research programs. As the Company pursues its ongoing and planned Zimura, HtrA1 inhibitor, RHO-adRP and BEST1 development programs and its collaborative gene therapy sponsored research programs, or as the Company commences any new development efforts in relation to additional product candidates that the Company may in-license or acquire as it pursues its business plan, the Company expects that its overall research and development expenses will increase from the current level of expenditure.

All research and development expenses are charged to operations as incurred in accordance with ASC 730, *Research and Development*. The Company accounts for non-refundable advance payments for goods and services that will be used in future research and development activities as expenses when the service has been performed or when the goods have been received, rather than when the payment is made.

Income Taxes

The Company utilizes the liability method of accounting for deferred income taxes, as set forth in ASC 740, *Income Taxes.* Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the carrying amounts and the tax basis of assets and liabilities.

Share-Based Compensation

The Company follows the provisions of ASC 718, *Compensation—Stock Compensation,* which requires the measurement and recognition of compensation expense for all share-based payment awards made to employees and non-employee directors, including employee stock options, restricted stock units ("RSUs") and the option granted to employees to purchase shares under the 2016 Employee Stock Purchase Plan (the "ESPP"). Share-based compensation expense is based on the grant date fair value estimated in accordance with the provisions of ASC 718 and is generally recognized as an expense over the requisite service period, net of estimated forfeitures. For grants containing performance-based vesting provisions, expense is recognized over the estimated achievement period.

Stock Options

The Company estimates the fair value of stock options granted to employees and non-employee directors on the date of grant using the Black-Scholes option-pricing model. Due to the lack of trading history, the Company's computation of stock-price volatility is based on the volatility rates of comparable publicly held companies over a period equal to the expected term of the options granted by the Company. The Company's computation of expected term is determined using the "simplified" method, which is the midpoint between the vesting date and the end of the contractual term. The Company believes that it does not have sufficient reliable exercise data in order to justify the use of a method other than the "simplified" method of estimating the expected exercise term of employee stock option grants. The Company utilizes a dividend yield of zero based on the fact that the Company has never paid cash dividends to stockholders and has no current intentions to pay cash dividends. The risk-free interest rate is based on the zero-coupon U.S. Treasury yield at the date of grant for a term equivalent to the expected term of the option.

(tabular dollars and shares in thousands, except per share data)

2. Summary of Significant Accounting Policies (Continued)

For stock options granted as consideration for services rendered by consultants, the Company recognizes expense in accordance with the requirements of ASC 505-50, *Equity Based Payments to Non-Employees*. Consultant stock option grants are recorded as an expense over the vesting period of the underlying stock options. At the end of each financial reporting period prior to vesting, the value of these options, as calculated using the Black-Scholes option-pricing model, will be re-measured using the fair value of the Company's common stock and the non-cash expense recognized during the period will be adjusted accordingly. Since the fair value of options granted to consultants is subject to change in the future, the amount of the future expense will include fair value re-measurements until the stock options are fully vested.

The weighted-average assumptions used to estimate grant date fair value of stock options using the Black-Scholes option pricing model were as follows for the years ended December 31, 2018, 2017 and 2016:

	Years ended December 31,		
	2018	2017	2016
Expected common stock price volatility	85%	81%	71%
Risk-free interest rate	2.39% - 2.95%	1.82% - 2.38%	1.14% - 2.37%
Expected term of options (years)	6.0	6.1	6.1
Expected dividend yield	—	—	—

RSUs

The Company estimates the fair value of RSUs granted to employees using the closing market price of the Company's common stock on the date of grant.

ESPP

In April 2016, the board of directors adopted the ESPP pursuant to which the Company may sell up to an aggregate of 1,000,000 shares of common stock. The ESPP was approved by the Company's stockholders in June 2016. The ESPP is considered compensatory and the fair value of the discount and look back provision are estimated using the Black-Scholes option-pricing model and recognized over the six month withholding period prior to purchase.

Share-based compensation expense includes expenses related to stock options and RSUs granted to employees, non-employee directors and consultants, as well as the option granted to employees to purchase shares under the ESPP, all of which have been reported in the Company's Statements of Operations as follows:

	Years ended December 31,		
	2018	2017	2016
Research and development	$ 4,967	$ 11,114	$ 21,380
General and administrative	6,105	7,057	10,280
Total	$ 11,072	$ 18,171	$ 31,660

Recently Adopted Accounting Pronouncements

In May 2014, the FASB issued ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). ASC 606 outlines a new, single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. This new revenue recognition model provides a five-step analysis in determining when and how revenue is recognized. The new model requires revenue recognition to depict the transfer of promised goods or services to customers in an amount that reflects the consideration a company expects to receive in exchange for those goods or services. On January 1, 2018, the Company adopted this guidance using the modified retrospective approach. Due to the termination of the Novartis Agreement and the Company's current lack of other revenue sources, the Company's financial statements were not impacted by adoption of this standard. The future impact of ASC 606 will be dependent on the nature of the Company's future revenue contracts and arrangements, if any.

2. Summary of Significant Accounting Policies (Continued)

In August 2016, the FASB issued Accounting Standards Update (ASU) No. 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*, which clarifies the presentation of certain specific cash flow issues in the Statement of Cash Flows. For public companies, the amendments are effective for annual reporting periods beginning after December 15, 2017, and interim periods within those annual periods. Early adoption is permitted. Starting with the three months ended March 31, 2018, the Company adopted this guidance. The adoption did not have a material impact on the Company's financial statements.

In January 2017, the FASB issued ASU No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business*, in an effort to clarify the definition of a business with the objective of adding guidance to assist entities with evaluating whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. The amendments of this ASU are effective for fiscal years beginning after December 15, 2017, and interim periods within those fiscal years. Early adoption is permitted. This new guidance was applicable for the acquisition of Inception 4 and will be applicable for any other acquisitions by the Company on or after January 1, 2018.

Recent Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-2, *Leases (Topic 842)*. Under the new guidance, lessees will be required to recognize the following for all leases (with the exception of short-term leases) at the commencement date: (1) a lease liability, which is a lessee's obligation to make lease payments arising from a lease, measured on a discounted basis; and (2) a right-of-use asset, which is an asset that represents the lessee's right to use, or control the use of, a specified asset for the lease term. Under the new guidance, lessor accounting is largely unchanged. Certain targeted improvements were made to align, where necessary, lessor accounting with the lessee accounting model and ASC 606. The new lease guidance simplified the accounting for sale and leaseback transactions primarily because lessees must recognize lease assets and lease liabilities. Lessees will no longer be provided with a source of off-balance sheet financing. Publicly-traded business entities should apply the amendments in ASU 2016-2 for fiscal years beginning after December 15, 2018 (i.e., January 1, 2019, for a calendar year entity), including interim periods within those fiscal years. Early application is permitted for all publicly-traded business entities and all non-publicly-traded business entities upon issuance. Lessees (for capital and operating leases) and lessors (for sales-type, direct financing, and operating leases) must apply a modified retrospective transition approach for leases existing at, or entered into after, the beginning of the earliest comparative period presented in the financial statements. The modified retrospective approach would not require any transition accounting for leases that expired before the earliest comparative period presented. Lessees and lessors may not apply a full retrospective transition approach. The Company has assessed the impact of adopting this new accounting guidance on its financial statements and footnote disclosures. As such, the Company expects the most significant impact will be the recognition of right-of-use assets and lease liabilities of approximately $1.5 million on its Consolidated Balance Sheet.

In June 2018, the FASB issued ASU No. 2018-07, *Improvements to Nonemployee Share-Based Payment Accounting,* which 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 employees and nonemployees. For public companies, the amendments are effective for annual reporting periods beginning after December 15, 2018, including interim periods within those annual periods. Early adoption is permitted, but no earlier than a company's adoption date of ASC 606. The Company is currently assessing the impact that adopting this new accounting guidance will have on its financial statements and footnote disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurement (Topic 820)*, which modifies the disclosure requirements on fair value measurements in Topic 820, Fair Value Measurement, including, among other changes, the consideration of costs and benefits when evaluating disclosure requirements. For public companies, the amendments are effective for annual reporting periods beginning after December 15, 2019, including interim periods within those annual periods. Early adoption is permitted. The Company is currently assessing the impact that adopting this new accounting guidance will have on its financial statements and footnote disclosures.

In August 2018, the FASB issued ASU No. 2018-15, *Intangibles - Goodwill and Other - Internal-Use Software* (Subtopic 350-40): *Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That Is a Service Contract* (a consensus of the FASB Emerging Issues Task Force). ASU 2018-15 aligns the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal-use

(tabular dollars and shares in thousands, except per share data)

2. Summary of Significant Accounting Policies (Continued)

software license). This guidance is effective for fiscal years beginning after December 15, 2019, and for interim periods within those fiscal years, with early adoption permitted.The Company is currently assessing the impact that adopting this new accounting guidance will have on its financial statements and footnote disclosures.

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements (Topic 808)*, which clarifies the interaction between the guidance for collaborative arrangements (Topic 808) and the new revenue recognition standard (Topic 606). For public companies, the amendments are effective for annual reporting periods beginning after December 15, 2019, including interim periods within those annual periods. Early adoption is permitted. The Company is currently assessing the impact that adopting this new accounting guidance will have on its financial statements and footnote disclosures.

3. Net Income (Loss) Per Common Share

Basic and diluted net income (loss) per common share is determined by dividing net income (loss) by the weighted average common shares outstanding during the period. For the periods when there is a net loss, stock options and RSUs have been excluded from the calculation of diluted net loss per common share because their effect would be anti-dilutive. Therefore, the weighted average common shares used to calculate both basic and diluted net loss per common share would be the same. The following table sets forth the computation of basic and diluted net income (loss) per common share for the periods indicated:

	Years ended December 31,		
	2018	2017	2016
Basic and diluted net income (loss) per common share calculation:			
Net income (loss)	$ 63,087	$ 114,205	$ (193,420)
Weighted average common shares outstanding - basic	37,061	35,919	35,486
Plus: net effect of dilutive stock options and unvested restricted stock units	27	88	—
Weighted average common shares outstanding - dilutive	37,088	36,007	35,486
Net income (loss) per common share - basic	$ 1.70	$ 3.18	$ (5.45)
Net income (loss) per common share - diluted	$ 1.70	$ 3.17	$ (5.45)

The following potentially dilutive securities have been excluded from the computations of diluted weighted average common shares outstanding for the periods presented, as they would be anti-dilutive:

	Years ended December 31,		
	2018	2017	2016
Stock options outstanding	5,873	5,179	3,359
Restricted stock units	601	182	721
Total	6,474	5,361	4,080

4. Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at the date of purchase to be cash equivalents. Cash and cash equivalents included cash of $4.4 million and $9.5 million at December 31, 2018 and 2017, respectively. Cash and cash equivalents at December 31, 2018 and December 31, 2017 also included $126.8 million and $157.4 million, respectively, of investments in money market funds and certain short-term investment-grade corporate debt securities with original maturities of 90 days or less.

The Company classifies its corporate debt securities within the fair value hierarchy as Level 2 assets, as it primarily utilizes quoted market prices or rates for similar instruments to value these securities.

(tabular dollars and shares in thousands, except per share data)

4. Cash and Cash Equivalents (Continued)

The following table presents, for each of the fair value hierarchy levels required under ASC 820, the Company's assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2018:

	Fair Value Measurement Using		
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
Assets			
Investments in money market funds*	$ 97,402	$ —	$ —
Investments in corporate debt securities*	$ —	$ 29,425	$ —

The following table presents, for each of the fair value hierarchy levels required under ASC 820, the Company's assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2017:

	Fair Value Measurement Using		
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
Assets			
Investments in money market funds*	$ 162,457	$ —	$ —

* Investments in money market funds and corporate debt securities with maturities less than 90 days are reflected in cash and cash equivalents in the accompanying Balance Sheets.

No transfer of assets between Level 1 and Level 2 of the fair value measurement hierarchy occurred during the years ended December 31, 2018 or December 31, 2017.

5. Inception 4 Acquisition

In October 2018, the Company entered into an Agreement and Plan of Merger (the “Inception 4 Merger Agreement”) by and among the Company, Orion Ophthalmology Merger Sub, Inc., a Delaware corporation and a direct, wholly owned subsidiary of the Company (“Merger Sub I”), Orion Ophthalmology LLC, a Delaware limited liability company and a direct, wholly owned subsidiary of the Company (“Orion”), Inception 4, a Delaware corporation, and, solely in its capacity as the representative, agent and attorney-in-fact of the equityholders of Inception 4, Fortis Advisors LLC, a Delaware limited liability company. Pursuant to the Inception 4 Merger Agreement, in October 2018, the Company acquired Inception 4 through the merger of Merger Sub I with and into Inception 4, with Inception 4 surviving as a direct, wholly owned subsidiary of the Company, and as part of the same overall transaction, the merger of Inception 4 with and into Orion, with Orion surviving as a direct, wholly owned subsidiary of the Company (the transactions are collectively referred to as the "Inception 4 Merger"). Prior to the Inception 4 Merger, Inception 4 was a privately held biotechnology company focused on the research and development of small molecule HtrA1 inhibitors for age-related retinal diseases in humans.

Pursuant to the terms of the Inception 4 Merger Agreement, as upfront consideration, the Company issued approximately 5.2 million shares of the Company’s common stock to the former equityholders of Inception 4, which were valued at approximately $11.7 million based on the acquisition date closing price of the Company’s common stock of $2.26 per share. Additionally, subject to the terms and conditions of the Inception 4 Merger Agreement, the former equityholders of Inception 4 will be entitled to receive contingent payments up to an aggregate of $105.0 million from the Company for the achievement of specified clinical and regulatory milestones, with $45 million of such potential payments relating to GA and $60 million of such potential payments relating to wet AMD. The future milestone payments will be payable in the form of shares of the Company's common stock, calculated based on the price of its common stock over a five-trading day period preceding the achievement of the relevant milestone, unless and until the issuance of such shares would, together with all other

5. Inception 4 Acquisition (Continued)

shares issued in connection with the Inception 4 Merger, exceed an overall maximum limit of approximately 7.2 million shares, which is equal to 19.9% of the number of issued and outstanding shares of the Company's common stock as of the close of business on the business day prior to the closing date, and will be payable in cash thereafter.

At closing, the Company acquired all of Inception 4's assets which included intellectual property and in-process research and development ("IPR&D") associated with Inception 4's HtrA1 inhibitor program and approximately $6.1 million in cash. There were no other tangible assets, leases or liabilities. The Company believes the cash it acquired in connection with its acquisition of Inception 4 will be sufficient to fund the majority of anticipated development costs associated with the development of the HtrA1 inhibitor program through the IND submission stage.

The Company evaluated the acquisition of Inception 4 under ASU No. 2017-01, Business Combinations: *Clarifying the Definition of a Business*. Based on the results of the analysis performed, the Company concluded that substantially all of the fair value of the gross assets acquired under the Inception 4 Merger Agreement is concentrated in a single identifiable asset. As a result, the Company concluded that the acquisition of Inception 4 does not represent an acquisition of a business and does not qualify as a business combination to be accounted for under ASC 805. Further, the Company concluded that the legal entity is not a variable interest entity under ASC 810 - *Consolidation*. Consequently, the Company concluded that the acquisition of Inception 4 should be accounted for as an asset acquisition under ASC 805-50. As the contingent consideration is not a derivative under ASC 815 - *Derivatives and Hedging*, any contingent payments will be recognized when earned or achieved and such amounts will be expensed upon payment for pre-commercial activities and capitalized for regulatory approvals and post-commercial activities. Further, as the acquired IPR&D has no alternative future use, in accordance with ASC 730, at closing, the Company charged to expense its allocated fair value of $6.9 million, which is the total acquisition consideration including transaction costs of $1.3 million less the cash acquired.

6. Licensing and Commercialization Agreements

RHO-adRP Gene Therapy Agreements with the University of Florida and the University of Pennsylvania

In June 2018, the Company entered into an exclusive global license agreement (the "RHO-adRP License Agreement") with UFRF and Penn (collectively, the "Licensors"). Under the agreement, the Licensors granted the Company a worldwide, exclusive license under specified patent rights and a worldwide, non-exclusive license under specified know-how, including specified preclinical data, to manufacture, develop and commercialize certain AAV gene therapy products for the treatment of rhodopsin-mediated diseases. The rights granted under the RHO-adRP License Agreement included certain patent rights covering a novel AAV gene therapy product candidate intended to treat RHO-adRP (the "RHO-adRP Licensed Product").

In June 2018, the Company paid UFRF, on behalf of both Licensors, a $0.5 million upfront license issuance fee in connection with entry into the agreement, which was recorded as a research and development expense, as well as accrued patent prosecution expenses of approximately $30 thousand, which was recorded as a general and administrative expense. Under the agreement, the Company agreed to pay an annual license maintenance fee in the low double-digit thousands of dollars, which will be payable on an annual basis until the first commercial sale of a licensed product. In addition, the Company agreed to reimburse UFRF for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

The Company further agreed to pay UFRF, on behalf of both Licensors, up to an aggregate of $23.5 million if the Company achieves specified clinical, marketing approval and reimbursement approval milestones with respect to a licensed product and additionally, up to an aggregate of $70.0 million if the Company achieves specified commercial sales milestones with respect to a licensed product.

The Company is also obligated to pay UFRF, on behalf of both Licensors, royalties at a low single-digit percentage of net sales of licensed products. Such royalties are subject to customary reductions for lack of patent coverage and loss of regulatory exclusivity. In addition, such royalties with respect to any licensed product in any country may be offset by a specified portion of any royalty payments actually paid by the Company with respect to such licensed product in such country under third-party licenses for patent rights or other intellectual property rights that are necessary to manufacture, develop and commercialize the licensed product in such country. The Company's obligation to pay royalties under the RHO-adRP License Agreement will continue on a licensed product-by-licensed product and country-by-country basis until the latest of:

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Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

6. Licensing and Commercialization Agreements (Continued)

- the expiration of the last-to-expire licensed patent rights covering a licensed product in the country of sale;
- the expiration of regulatory exclusivity covering a licensed product in the country of sale; and
- ten years from the first commercial sale of the applicable licensed product in the country of sale.

Beginning on the earlier of (i) the calendar year following the first commercial sale of a licensed product and (ii) the first business day of 2031, the Company is also obligated to pay certain minimum royalties, not to exceed an amount in the low hundreds of thousands of dollars on an annual basis, which minimum royalties are creditable against the Company's royalty obligation with respect to net sales of licensed products due for the year in which the minimum royalty is paid.

In addition, if the Company or an affiliate sublicenses any of the licensed patent rights to a third party, the Company will be obligated to pay UFRF, on behalf of both Licensors, a low double-digit percentage of the consideration received in exchange for such sublicense. If the Company receives a rare pediatric disease priority review voucher from the U.S. Food and Drug Administration ("FDA") in connection with obtaining marketing approval for a licensed product and the Company subsequently uses such priority review voucher in connection with a different product candidate or sells such priority review voucher, the Company will be obligated to make certain payments to UFRF, on behalf of both Licensors.

Unless earlier terminated by the Company, the RHO-adRP License Agreement will expire upon the expiration of the Company’s obligation to pay royalties to UFRF on net sales of licensed products. The Company may terminate the agreement at any time for any reason upon prior written notice to UFRF. Penn or UFRF may terminate the RHO-adRP License Agreement in the event of certain breaches by the Company or in the event of certain insolvency events regarding the Company.

In addition to the exclusive license agreement, the Company and Penn also agreed to a Master-Sponsored Research Agreement (the "MSRA"), facilitated by the Penn Center for Innovation. Under the MSRA, the Company and Penn are conducting additional preclinical studies for the RHO-adRP Licensed Product, as well as a natural history study of RHO-adRP patients.

Prior Licensing and Commercialization Agreement with Novartis Pharma AG

Prior to 2018, the Company's revenue resulted from payments received under the Novartis Agreement, as modified by the July 2017 Letter Agreement. These two agreements are described below. The Company used the relative selling price method to allocate arrangement consideration to the Company’s performance obligations under the Novartis Agreement. The Company completed the deliverables under the Novartis Agreement and the July 2017 Letter Agreement during the third quarter of 2017.

In May 2014, the Company entered into the Novartis Agreement. Under the Novartis Agreement, the Company granted Novartis exclusive rights under specified patent rights, know-how and trademarks controlled by the Company to manufacture standalone Fovista products and products combining Fovista with an anti-VEGF agent to which Novartis has rights in a co-formulated product, for the treatment, prevention, cure or control of any human disease, disorder or condition of the eye, and to develop and commercialize those licensed products in all countries outside of the United States (the “Novartis Territory”). The Company agreed to use commercially reasonable efforts to complete its ongoing pivotal Phase 3 clinical program for Fovista and Novartis agreed to use commercially reasonable efforts to develop a standalone Fovista product and a co-formulated product containing Fovista and an anti-VEGF agent to which Novartis has rights, and to use commercially reasonable efforts, subject to obtaining marketing approval, to commercialize licensed products in the Novartis Territory in accordance with agreed development and marketing plans.

In July 2017, the Company and Novartis entered into the July 2017 Letter Agreement to streamline the process and timeline for evaluating data from the OPH1004 trial once it became available. In October 2017, following the failure of the Phase 3 Fovista program and pursuant to the terms of the July 2017 Letter Agreement, Novartis elected to terminate the Novartis Agreement with immediate effect.

In May 2014, Novartis paid the Company a $200.0 million upfront payment. In each of September 2014 and March 2015, the Company achieved, and Novartis paid the Company, a $50.0 million enrollment-based milestone, and in June 2016, the Company achieved, and Novartis paid the Company, a $30.0 million enrollment-based milestone, for an aggregate total of

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Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

6. Licensing and Commercialization Agreements (Continued)

$130.0 million in enrollment-based milestones under the Novartis Agreement. The Company used the relative selling price method to allocate these payments to contract deliverables based on its performance obligations under the Novartis Agreement.

Activities under the Novartis Agreement were evaluated under ASC 605-25, *Revenue Recognition—Multiple Element Arrangements* ("ASC 605-25") (as amended by ASU 2009-13, *Revenue Recognition* ("ASU 2009-13")) to determine if they represented a multiple element revenue arrangement. The Novartis Agreement included the following deliverables: (1) an exclusive license to commercialize Fovista outside the United States (the "License Deliverable"); (2) the performance obligation to conduct research and development activities related to the Phase 3 Fovista clinical trials and certain Phase 2 trials for Fovista (the "R&D Activity Deliverable"); (3) the performance obligation to supply API to Novartis for development and manufacturing purposes (the "Manufacturing Deliverable") and (4) the Company's obligation to participate on the joint operating committee established under the terms of the Novartis Agreement and related subcommittees (the "Joint Operating Committee Deliverable"). The Company's obligation to provide access to clinical and regulatory information as part of the License Deliverable included the obligation to provide access to all clinical data, regulatory filings, safety data and manufacturing data to Novartis which was necessary for the commercialization of Fovista in the Novartis Territory. The R&D Activity Deliverable included the right and responsibility for the Company to conduct the Phase 3 Fovista clinical program and other Phase 2 studies of Fovista which were necessary or desirable for regulatory approval or commercialization of Fovista. The Manufacturing Deliverable included the obligation for the Company to supply API to Novartis for clinical purposes, for which Novartis agreed to pay the Company's manufacturing costs. The Joint Operating Committee Deliverable included the obligation to participate in the Joint Operating Committee and related subcommittees at least through the first anniversary of regulatory approval in the European Union. All of these deliverables were deemed to have stand-alone value and to meet the criteria to be accounted for as separate units of accounting under ASC 605-25. Factors considered in this determination included, among other things, the subject of the licenses and the research and development and commercial capabilities of Novartis. Accordingly, each unit was accounted for separately.

The Novartis Agreement included a termination right for the Company in the event that specified governmental actions prevented the parties from materially progressing the development or commercialization of licensed products. If the Company elected to exercise this termination option, it would have been required to pay a substantial termination fee equivalent to the entire upfront payment amount. The Company concluded that this termination provision constituted a contingent event that was unknown at the inception of the agreement. As such, the Company recorded the $200.0 million upfront payment in deferred revenue, long-term until such time that the contingency related to this termination provision was resolved. In July 2017, the contingency was resolved when the Company permanently waived this termination right as part of the July 2017 Letter Agreement.

The July 2017 Letter Agreement also provided Novartis with a shorter notice period in the event Novartis determined to terminate the Novartis Agreement in certain circumstances. In addition, the July 2017 Letter Agreement provided Novartis with a fully paid-up, royalty free license to use data from the Lucentis monotherapy arms of the Company's Phase 2b OPH1001 trial and Phase 3 OPH1002 and OPH1003 trials in the Novartis Territory in connection with the development, manufacturing and commercialization of Novartis-controlled anti-VEGF products. The Lucentis study data license continues until July 3, 2022.

The Company evaluated the July 2017 Letter Agreement under ASC 605-25 and determined that the July 2017 Letter Agreement does not create any new deliverables. The Company is treating the Fovista license granted at the inception of the Novartis Agreement and the Lucentis study data license granted under the July 2017 Letter Agreement as one collective technology license (the "Licenses") delivered at the inception of the Novartis Agreement. In addition, as the waiver of its right to terminate the Novartis Agreement as a result of specified governmental actions resolved the Company's contingency with respect to such termination right and the associated termination fee, the Company allocated the entire previously deferred amount, $200.0 million, to the deliverables that were determined based on the relative selling price at contract inception. Upon entry into the July 2017 Letter Agreement in July 2017, the Company immediately recognized as revenue $189.8 million of the upfront payment allocated to contract deliverables completed during prior periods. Upon termination of the OPH1004 trial in August 2017, the Company recognized the remaining $16.9 million of collaboration revenue, attributable to the R&D Deliverable, previously deferred under the Novartis Agreement. In total, during the third quarter of 2017, the Company

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

6. Licensing and Commercialization Agreements (Continued)

recognized $206.7 million in previously deferred collaboration revenue in connection with the Novartis Agreement. The recognition of this revenue did not impact the Company's cash balance.

Below is a summary of the components of the Company's collaboration revenue for the years ended December 31, 2018, 2017, and 2016:

	Years ended December 31,		
	2018	2017	2016
License revenue	$ —	$ 152,912	$ 22,937
Research and development activity revenue	—	56,180	9,741
API transfer revenue	—	754	18,212
Joint operating committee revenue	—	131	19
Total collaboration revenue	$ —	$ 209,977	$ 50,909

7. Financing Agreement with Novo Holdings A/S

In May 2013, the Company entered into a Purchase and Sale Agreement (the "Novo Agreement") with Novo Holdings A/S (formerly Novo A/S), pursuant to which the Company obtained financing in three tranches in an aggregate amount equal to $125.0 million in return for the sale to Novo Holdings A/S of aggregate royalties of a mid-single digit percentage on worldwide sales of (a) Fovista, (b) certain Fovista-related Products ("Fovista-Related Products"), and (c) certain other antagonists of platelet-derived growth factor ("PDGF"), if any, that the Company initiated development activities for prior to the fifth anniversary of the Novo Agreement (collectively, the "Anti-PDGF Royalty Products").

Pursuant to the Novo Agreement, in each of May 2013, January 2014 and November 2014, the Company received cash payments of $41.7 million, or $125.0 million in the aggregate, and Novo Holdings A/S received, in the aggregate, a right to receive royalties on net sales of Fovista at a mid-single digit percentage.

The $125.0 million in aggregate proceeds from the three financing tranches under the Novo Agreement represented the full funding available under the Novo Agreement, and prior to December 31, 2018, was recorded as a royalty purchase liability on the Company's Balance Sheet, in accordance with ASC 730, *Research and Development*. Because there was a significant related party relationship between the Company and Novo Holdings A/S, the Company treated its obligation to make royalty payments under the Novo Agreement as an implicit obligation to repay the funds advanced by Novo Holdings A/S.

On December 31, 2018, the Company and Novo Holdings A/S entered into a letter agreement (the "Novo Termination Agreement"), that terminated the Novo Agreement. As a result of the Novo Termination Agreement, Novo Holdings A/S relinquished all rights to receive royalties based on net sales of Anti-PDGF Royalty Products. In exchange, the Company agreed to forbear from any future filing, prosecution, maintenance or enforcement of any intellectual property rights related to Anti-PDGF Royalty Products, and from granting any third party or affiliate any right or license in any such intellectual property rights or clinical study data generated by or on behalf of the Company, its affiliates or licensees or sublicensees, for the development, manufacture or commercialization of Anti-PDGF Royalty Products or any other antagonists of PDGF. The foregoing restriction does not apply to gene therapies (so long as the Company does not grant any rights or licenses to intellectual property or clinical study data related to Fovista or Fovista-Related Products). The Company further agreed, until December 31, 2028, not to develop, manufacture, seek or obtain regulatory approval for, or commercialize Anti-PDGF Royalty Products without the prior written consent of Novo Holdings A/S. The foregoing restriction does not apply to any gene therapies (so long as the Company does not utilize data related to Fovista or Fovista-Related Products).

As a result of the Novo Termination Agreement, the Company has no legal obligation to repay Novo the $125.0 million through future product royalties or any other development activities. Accordingly, the Company extinguished the $125.0 million royalty purchase liability from its Consolidated Balance Sheet at December 31, 2018 and recognized a related gain of $125.0 million in its Consolidated Statements of Operations for the year ended December 31, 2018. As the Company had received the proceeds related to the royalty purchase liability in prior periods, the extinguishment of the royalty purchase liability and the related gain did not impact the Company's cash balance during this period.

8. Property and Equipment

Property and equipment as of December 31, 2018 and 2017 were as follows:

	Useful Life (Years)	December 31, 2018	December 31, 2017
Manufacturing and clinical equipment	7 - 10	$ 412	$ 412
Computer, software and other office equipment	5	933	933
		1,345	1,345
Accumulated depreciation		(1,010)	(827)
Property and equipment, net		$ 335	$ 518

For the years ended December 31, 2018, 2017 and 2016, depreciation expense was $0.2 million, $2.8 million and $0.8 million, respectively.

9. Income Taxes

In December 2017, the U.S. Tax Cuts and Jobs Act (“TCJA”) was enacted reducing the corporate tax rate from 35% to 21% effective for tax years beginning on or after January 1, 2018. ASC 740, *Income Taxes* requires the effects of changes in tax laws to be recognized in the period in which the legislation is enacted. However, due to the complexity and significance of the TCJA’s provisions, the SEC staff issued SAB 118, which allows companies to record the tax effects of the TCJA on a provisional basis based on a reasonable estimate, and then, if necessary, subsequently adjust such amounts during a limited measurement period as more information becomes available. The Company recorded provisional amounts and has subsequently finalized its accounting analysis based on the guidance, interpretations, and data available as of December 31, 2018.

Under the TCJA, the Corporate Alternative Minimum Tax ("AMT") was repealed. The Company's previously recorded AMT credits of approximately $3.5 million are now refundable over a four-year period beginning in 2018 and the previously recorded valuation allowance for these AMT credits was reversed during the year ended December 31, 2017. The Company does not have any offshore earnings from which to record the mandatory transition tax.

The Company utilizes the liability method of accounting for deferred income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the carrying amounts and the tax basis of assets and liabilities. A valuation allowance is established against deferred tax assets when, based on the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The Company's policy is to record interest and penalties on uncertain tax positions as income tax expense.

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

9. Income Taxes (Continued)

Deferred income taxes reflect the net effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. A reconciliation of the statutory U.S. federal rate to the Company's effective tax rate is as follows:

	Years ended December 31,		
	2018	2017	2016
Percent of pre-tax income:			
U.S. federal statutory income tax rate	21.0 %	35.0 %	35.0 %
State taxes, net of federal benefit	18.5 %	14.6 %	2.8 %
Permanent items	4.0 %	4.0 %	(1.4)%
Remeasurement of deferred tax assets	— %	49.9 %	— %
Impact of state rate changes	(0.2)%	(27.9)%	(11.0)%
Research and development credit	(2.4)%	— %	1.9 %
Alternative minimum tax credit	— %	(1.3)%	1.1 %
Change in valuation allowance	(42.6)%	(78.6)%	(28.2)%
Effective income tax rate	(1.7)%	(4.3)%	0.2 %

The components of income tax benefit are as follows:

	Years ended December 31,		
	2018	2017	2016
Current:			
Federal	$ —	$ 173	$ (23,393)
State	(1,063)	(1,356)	21
Deferred:			
Federal	—	(3,529)	22,966
State	—	—	—
Income tax benefit	$ (1,063)	$ (4,712)	$ (406)

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

9. Income Taxes (Continued)

Significant components of the Company's deferred tax assets (liabilities) for 2018 and 2017 consist of the following:

	As of December 31,	
	2018	2017
Deferred tax assets (liabilities)		
Deferred revenue	$ —	$ 40,961
License and technology payments	7,221	8,222
Share-based compensation	20,342	17,599
Accrued expenses	371	608
Depreciation	(28)	81
Federal and state net operating loss carryforwards	88,766	76,309
Research and development credits	5,933	3,782
Other	5	3,534
Deferred income tax assets	122,610	151,096
Valuation allowance	(122,610)	(147,567)
Net deferred tax assets	$ —	$ 3,529

The Company considers whether it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of taxable income during the periods in which the temporary differences representing net future deductible amounts become deductible.

The Company incurred tax losses in 2018 and 2017. The Company realized its net deferred tax assets recorded as of December 31, 2017 in 2016 as a result of the Company’s carry back of its 2015 federal tax losses to 2014. The Company has carried forward its 2015 state tax losses due to various state restrictions on the use of carryback claims. The state NOLs are expected to begin to expire in 2027. Due to the Company’s history of losses and lack of other positive evidence to support taxable income after the 2014 tax year, the Company has recorded a valuation allowance against those remaining deferred tax assets that are not expected to be realized. As of December 31, 2018, the Company has federal NOL carryforwards of approximately $315.5 million. These losses are due to expire in 2036 and 2037.

For the year ended December 31, 2018, the Company recorded a benefit from income of $1.1 million which primarily related to the settlement of a local tax audit. For the year ended December 31, 2017, the Company recorded a benefit from income of $4.7 million which was related to a $3.5 million reduction in its valuation allowances for AMT credits to reflect the impact of the TCJA enactment and the settlement of a state franchise tax audit for $1.4 million, partially offset by the reversal of previously recorded benefits related to the change in unrealized gains of the Company's investment portfolio. During 2018, the Company reclassified the $3.5 million related to AMT credits to a non-current income tax receivable as it expects to receive the refunds over the next four years.

Although the Company generated net income before income taxes for the years ended December 31, 2018 and 2017, this income is due to the Novo Termination Agreement and the July 2017 Letter Agreement with Novartis which had previously been recorded on the Company's federal and state income tax returns. This recognition of income resulted in the reduction of a deferred tax asset that was completely offset by a previously recorded valuation allowance. With respect to the remaining deferred tax assets, except for the AMT credits previously discussed above, there was no change in the amount of assets realizable at December 31, 2018.

In the second quarter of 2017, the IRS concluded an audit of the Company’s U.S. federal income tax returns for the years 2013, 2014 and 2015, resulting in an immaterial amount of additional tax due. Federal NOLs for 2016 and general business credits generated between 2007 and 2016 remain subject to audit.

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

9. Income Taxes (Continued)

Pursuant to ASC 740, *Income Taxes*, the Company routinely evaluates the likelihood of success if challenged on income tax positions claimed on its income tax returns. During the year ended December 31, 2018, the Company reduced certain deferred tax assets by $25.0 million and reduced the corresponding valuation allowance by an equivalent amount. Additionally, the Company amended certain state income tax returns to claim a refund for taxes previously paid. These claims may result in refunds to the Company of up to approximately $5.0 million. These items have not been recognized in the financial statements and if disallowed by the tax authorities, would not result in an adjustment to the Company's effective tax rate, its balance sheet or its cash flow statements for the current year.

The Company's position with respect to uncertain tax positions is set forth below:

Opening balance	$	16,881
Gross amount of increases in unrecognized tax benefits during the period - current year provisions		—
Gross amount of increases in unrecognized tax benefits during the period - prior year provisions		17
Gross amount of decreases in unrecognized tax benefits during the period - other		(1,413)
Decreases due to settlement with tax authorities during the period		(1,502)
Reduction of unrecognized tax benefits due to expiration of the state of limitations during the period		—
Closing Balance	$	13,983

As the Company is currently being audited by the New Jersey Division of Taxation, an estimate of unrecognized tax benefits that may be realized over the next twelve months is expected to be in the range of zero to approximately $5.0 million.

The Company will continue to evaluate its ability to realize its deferred tax assets on a periodic basis and will adjust such amounts in light of changing facts and circumstances including, but not limited to, future projections of taxable income, tax legislation, rulings by relevant tax authorities, the progress of ongoing tax audits and the regulatory approval of product candidates currently under development. Any additional changes to the valuation allowance recorded on deferred tax assets in the future would impact the Company's income taxes.

10. Operating Leases

The Company leases office space located in New York, New York and Princeton, New Jersey under operating lease arrangements. The lease for the Company's New York office space expires at the end of June 2020, whereas the sublease for the Company's Princeton office space expires in March 2020. Future minimum rental commitments under non-cancelable operating leases in effect as of December 31, 2018, are as follows:

2019	$	1,040
2020		504
Total	$	1,544

Rent expense is calculated on the straight-line basis and amounted to $0.8 million, $3.6 million and $3.0 million for the years ended December 31, 2018, 2017 and 2016, respectively.

11. Commitments and Contingencies

Archemix Corp.

The Company is party to an agreement (the "C5 License Agreement") with Archemix Corp. ("Archemix"), under which the Company in-licensed rights in certain patents, patent applications and other intellectual property related to Zimura and pursuant to which the Company may be required to pay sublicense fees and make milestone payments. Under the C5 License Agreement, for each anti-C5 aptamer product that the Company may develop under the agreement, including Zimura, the Company is obligated to make payments to Archemix of up to an aggregate of $57.5 million if the Company achieves

11. Commitments and Contingencies (Continued)

specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $24.5 million of such payments relating to second and third indications and $2.5 million of such payments relating to sustained delivery applications. Under the C5 License Agreement, the Company is also obligated to make additional payments to Archemix of up to an aggregate of $22.5 million if the Company achieves specified commercial milestones based on net product sales of all anti-C5 products licensed under the agreement. The Company is also obligated to pay Archemix a double-digit percentage of specified non-royalty payments the Company may receive from any sublicensee of its rights under the C5 License Agreement. The Company is not obligated to pay Archemix a running royalty based on net product sales in connection with the C5 License Agreement.

University of Florida and the University of Pennsylvania

Under the RHO-adRP License Agreement, the Company is obligated to make payments to UFRF, on behalf of both Licensors, of up to an aggregate of $23.5 million if the Company achieves specified clinical, marketing approval and reimbursement approval milestones with respect to a licensed product and up to an aggregate of an additional $70.0 million if the Company achieves specified commercial sales milestones with respect to a licensed product. The Company is also obligated to pay UFRF, on behalf of both Licensors, a running royalty equal to a low single-digit percentage of net sales of licensed products. The Company is also obligated to pay UFRF, on behalf of both Licensors, a double-digit percentage of specified non-royalty payments the Company may receive from any third party sublicensee of the licensed patent rights. Further, if the Company receives a rare pediatric disease priority review voucher from the FDA in connection with obtaining marketing approval for a licensed product and the Company subsequently uses such priority review voucher in connection with a different product candidate, the Company will be obligated to pay UFRF, on behalf of both Licensors, aggregate payments in the low double-digit millions of dollars based on certain approval and commercial sales milestones with respect to such other product. In addition, if the Company sells such a priority review voucher to a third party, the Company will be obligated to pay UFRF, on behalf of both Licensors, a low double-digit percentage of any consideration received from such third party in connection with such sale.

Former Equityholders of Inception 4

Under the Inception 4 Merger Agreement, the Company is obligated to make payments to the former equityholders of Inception 4 of up to an aggregate of $105 million, subject to the terms and conditions of the Inception 4 Merger Agreement, if the Company achieves certain specified clinical and regulatory milestones with respect to a product candidate from its HtrA1 inhibitor program, with $45 million of such potential payments relating to GA and $60 million of such potential payments relating to wet AMD. Under the Inception 4 Merger Agreement, the Company does not owe any commercial milestones or royalties based on net sales. The future milestone payments will be payable in the form of shares of the Company's common stock, calculated based on the price of its common stock over a five-trading day period preceding the achievement of the relevant milestone, unless and until the issuance of such shares would, together with all other shares issued in connection with the Inception 4 Merger, exceed an overall maximum limit of approximately 7.2 million shares, which is equal to 19.9% of the number of issued and outstanding shares of the Company's common stock as of the close of business on the business day prior to the closing date, and will be payable in cash thereafter. The Inception 4 Merger Agreement also includes customary indemnification obligations to the former equityholders of Inception 4, including for breaches of the representations and warranties, covenants and agreements of the Company and its subsidiaries (other than Inception 4) in the Inception 4 Merger Agreement.

Employment Contracts

The Company also has letter agreements with certain employees that require the funding of a specific level of payments, if certain events, such as a termination of employment in connection with a change in control or termination of employment by the employee for good reason or by the Company without cause, occur.

Contract Service Providers

In addition, in the course of normal business operations, the Company has agreements with contract service providers to assist in the performance of the Company’s research and development and manufacturing activities. Expenditures to CROs, CMOs and academic research institutions represent significant costs in preclinical and clinical development. Subject to required notice periods and the Company’s obligations under binding purchase orders and any cancellation fees that the Company may

11. Commitments and Contingencies (Continued)

be obligated to pay, the Company can elect to discontinue the work under these agreements at any time.

Legal Proceedings

On January 11, 2017, a putative class action lawsuit was filed against the Company and certain of its current and former executive officers in the United States District Court for the Southern District of New York, captioned Frank Micholle v. Ophthotech Corporation, et al., No. 1:17-cv-00210. On March 9, 2017, a related putative class action lawsuit was filed against the Company and the same group of its current and former executive officers in the United States District Court for the Southern District of New York, captioned Wasson v. Ophthotech Corporation, et al., No. 1:17-cv-01758. These cases were consolidated on March 13, 2018. On June 4, 2018, the lead plaintiff filed a consolidated amended complaint (the "CAC"). The CAC purports to be brought on behalf of shareholders who purchased the Company's common stock between March 2, 2015 and December 12, 2016. The CAC generally alleges that the Company and certain of its officers violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements concerning the results of the Company's Phase 2b trial and the prospects of the Company's Phase 3 trials for Fovista in combination with anti-VEGF agents for the treatment of wet AMD. The CAC seeks unspecified damages, attorneys' fees, and other costs. The Company and individual defendants filed a motion to dismiss the CAC on July 27, 2018. That motion is fully briefed.

On February 7, 2018, a shareholder derivative action was filed against the members of the Company's Board of Directors in the New York Supreme Court Commercial Division, captioned Cano v. Guyer, et al., No. 650601/2018. The complaint alleges that the defendants breached their fiduciary duties to the Company by adopting a compensation plan that overcompensates the non-employee members of the Board relative to boards of companies of comparable market capitalization and size. The complaint also alleges that the defendants were unjustly enriched as a result of the alleged conduct. The complaint purports to seek unspecified damages, on behalf of the Company, attorneys' fees, and other costs, as well as an order directing the Company to reform and improve its corporate governance and internal procedures to comply with applicable laws. The Company filed a motion to dismiss this case on May 14, 2018. On June 4, 2018, the plaintiff filed an amended complaint. On June 25, 2018, the Company filed a renewed motion to dismiss this case. On December 3, 2018, the parties filed a stipulation of settlement that contemplates that the Company will adopt certain compensation-related governance reforms and does not obligate the defendants or the Company to pay any monetary damages. In addition, the Company expects it may be liable to pay approximately $0.3 million in fees to plaintiff's counsel. A hearing to determine whether the court will approve the settlement is scheduled for March 12, 2019.

On August 31, 2018, a shareholder derivative action was filed against current and former members of the Company's Board of Directors and certain current and former officers of the Company in the United States District Court for the Southern District of New York, captioned Luis Pacheco v. David R. Guyer, et al., Case No. 1:18-cv-07999. The complaint, which is based substantially on the facts alleged in the CAC, alleges that the defendants breached their fiduciary duties to the Company and wasted the Company's corporate assets by failing to oversee the Company's business, and also alleges that the defendants were unjustly enriched as a result of the alleged conduct, including through receipt of bonuses, stock options and similar compensation from the Company, and through sales of the Company's stock between March 2, 2015 and December 12, 2016. The complaint purports to seek unspecified damages on the Company's behalf, attorneys' fees, and other costs, as well as an order directing the Company to reform and improve its corporate governance and internal procedures to comply with applicable laws, including submitting certain proposed amendments to the Company's corporate charter, bylaws and corporate governance policies for vote by the Company's stockholders. On December 14, 2018, the Company filed a motion to dismiss the complaint. The plaintiff filed its opposition to the motion to dismiss on February 22, 2019, and the Company's reply is due on April 3, 2019.

On October 16, 2018, the Company's board of directors received a shareholder demand to investigate and commence legal proceedings against certain members of the Company's board of directors. The demand alleges facts that are substantially similar to the facts alleged in the CAC and the Pacheco complaint and asserts claims that are substantially similar to the claims asserted in the Pacheco complaint. On January 30, 2019, the Company's board of directors received a second shareholder demand from a different shareholder to investigate and commence legal proceedings against certain current and former members of the Company's board of directors based on allegations that are substantially similar to the allegations contained in the first demand letter.

11. Commitments and Contingencies (Continued)

The Company denies any and all allegations of wrongdoing and intends to vigorously defend against these lawsuits. The Company is unable, however, to predict the outcome of these matters at this time. Moreover, any conclusion of these matters in a manner adverse to the Company and for which it incurs substantial costs or damages not covered by the Company's directors' and officers' liability insurance would have a material adverse effect on its financial condition and business. In addition, the litigation could adversely impact the Company's reputation and divert management's attention and resources from other priorities, including the execution of its business plan and strategies that are important to the Company's ability to grow its business, any of which could have a material adverse effect on the Company's business.

12. Stock Option and Compensation Plans

The Company adopted its 2007 Stock Incentive Plan (the "2007 Plan") for employees, non-employee directors and consultants for the purpose of advancing the interests of the Company's stockholders by enhancing its ability to attract, retain and motivate persons who are expected to make important contributions to the Company. The 2007 Plan provided for the granting of stock option awards, RSUs, and other stock-based and cash-based awards. Following the effectiveness of the 2013 Stock Incentive Plan described below in connection with the closing of the Company's initial public offering, the Company is no longer granting additional awards under the 2007 Plan.

In August 2013, the Company's board of directors adopted, and the Company's stockholders approved, the 2013 Stock Incentive Plan (the "2013 Plan"), which became effective immediately prior to the closing of the Company's initial public offering. In June 2015, the Company's board of directors adopted a first amendment to the 2013 Plan. The 2013 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, RSUs, restricted stock awards and other stock-based awards. Upon the effectiveness of the 2013 Plan, the number of shares of the Company's common stock that were reserved for issuance under the 2013 Plan was the sum of (1) a number of shares (up to a maximum of approximately 3,359,641 shares) that is equal to the sum of 739,317 shares (the number of shares of the Company's common stock then available for issuance under the 2007 Plan), and such number of shares of the Company's common stock that are subject to outstanding awards under the 2007 Plan that expire, terminate or are otherwise surrendered, canceled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right, plus (2) an annual increase, to be added the first business day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until, and including, the fiscal year ending December 31, 2023, equal to the lowest of 2,542,372 shares of the Company's common stock, 4% of the number of shares of the Company's common stock outstanding on the first day of the fiscal year and an amount determined by its board of directors. The Company's employees, officers, directors, consultants and advisors are eligible to receive awards under the 2013 Plan. However, incentive stock options may only be granted to employees of the Company.

Annual increases under the evergreen provisions of the 2013 Plan have resulted in the addition of an aggregate of approximately 8,554,000 additional shares to the 2013 Plan, including for 2019, an increase of approximately 1,656,000 shares, or 4% of the total number of shares of the Company's common stock outstanding as of January 1, 2019. As of December 31, 2018, the Company had approximately 840,000 shares available for grant under the 2013 Plan.

In April 2016, the board of directors adopted the ESPP pursuant to which the Company may sell up to an aggregate of 1,000,000 shares of common stock. The ESPP was approved by the Company's stockholders in June 2016. The ESPP allows eligible employees to purchase common stock at a price per share equal to 85% of the lower of the fair market value of the common stock at the beginning or end of each six month offering period during the term of the ESPP. The first offering period began in September 2016.

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Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

12. Stock Option and Compensation Plans (Continued)

A summary of the stock option activity, weighted average exercise prices, options outstanding and exercisable as of December 31, 2018, 2017 and 2016 is as follows (in thousands except weighted average exercise price):

	Years ended December 31,					
	2018		2017		2016	
	Common Stock Options	Weighted Average Exercise Price	Common Stock Options	Weighted Average Exercise Price	Common Stock Options	Weighted Average Exercise Price
Outstanding, December 31, 2017	5,284	$ 19.58	3,359	$ 39.92	3,009	$ 30.43
Granted	1,293	$ 1.67	3,024	$ 3.50	972	$ 60.40
Exercised	—	$ —	(20)	$ 1.64	(428)	$ 15.73
Expired or forfeited	(674)	$ 36.54	(1,079)	$ 38.17	(194)	$ 48.63
Outstanding, December 31, 2018	5,903	$ 13.72	5,284	$ 19.58	3,359	$ 39.92

	Years ended December 31,		
	2018	2017	2016
Options exercisable at December 31, 2018	2,709	1,954	1,531
Weighted average grant date fair value (per share) of options granted during the period	$ 1.20	$ 2.45	$ 38.18

As of December 31, 2018, there were approximately 5,615,000 options outstanding, net of estimated forfeitures, that had vested or are expected to vest. The weighted-average exercise price of these options was $14.17 per option; the weighted-average remaining contractual life of these options was 7.8 years; and the aggregate intrinsic value of these options was de minimis. A summary of the stock options outstanding and exercisable as of December 31, 2018 is as follows (in thousands except exercise prices and weighted average exercise price):

	December 31, 2018				
		Options Outstanding		Options Exercisable	
Range of Exercise Prices	Total Options Outstanding	Weighted Average Remaining Life (Years)	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$0.12-$10.03	4,231	8.8	$ 3.07	1,174	$ 4.20
$10.04-$20.00	133	4.5	$ 13.68	133	$ 13.68
$20.01-$30.00	114	4.4	$ 24.69	114	$ 24.69
$30.01-$40.00	680	4.4	$ 33.12	680	$ 33.12
$40.01-$55.00	508	6.6	$ 46.61	420	$ 46.48
$55.01-$73.22	237	7.0	$ 72.32	188	$ 72.09
	5,903	7.9	$ 13.72	2,709	$ 24.07
Aggregate Intrinsic Value	$ 3			$ 3	

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

12. Stock Option and Compensation Plans (Continued)

Cash proceeds from, and the aggregate intrinsic value of, stock options exercised during the years ended December 31, 2018, 2017 and 2016, respectively, were as follows:

	Years ended December 31,		
	2018	2017	2016
Cash proceeds from options exercised	$ —	$ 33	$ 6,934
Aggregate intrinsic value of options exercised	$ —	$ 43	$ 14,439

In connection with stock option awards granted to employees, the Company recognized approximately $7.6 million, $13.1 million and $22.8 million in share-based compensation expense during the years ended December 31, 2018, 2017 and 2016, respectively, net of expected forfeitures. As of December 31, 2018, there were approximately $9.0 million of unrecognized compensation costs, net of estimated forfeitures, related to stock option awards granted to employees, which are expected to be recognized over a remaining weighted average period of 2.1 years.

In connection with stock option awards granted to consultants, the Company recognized approximately $0.2 million, $0.3 million and $1.7 million in share-based compensation expense during the years ended December 31, 2018, 2017 and 2016, respectively, net of expected forfeitures. As of December 31, 2018, there were approximately $0.2 million of unrecognized compensation costs, net of estimated forfeitures, related to stock option awards granted to consultants, which are expected to be recognized over a remaining weighted average period of 1.7 years.

The following table presents a summary of the Company's outstanding RSU awards granted as of December 31, 2018 (in thousands except weighted average grant-date fair value):

	Restricted Stock Units	Weighted Average Grant-Date Fair Value
Outstanding, December 31, 2017	327	$ 51.08
Awarded	499	$ 1.45
Vested	(80)	$ 46.25
Forfeited	(67)	$ 45.57
Outstanding, December 31, 2018	679	$ 15.61

As of December 31, 2018, there were approximately 550,000 RSUs outstanding, net of estimated forfeitures, that are expected to vest. The weighted-average fair value of these RSUs was $10.36 per share; and the aggregate intrinsic value of these RSUs was approximately $0.7 million.

In connection with RSUs granted to employees, the Company recognized approximately $3.3 million, $4.4 million and $6.9 million in share-based compensation expense during the years ended December 31, 2018, 2017 and 2016, respectively, net of expected forfeitures. As of December 31, 2018, there was approximately $3.2 million of unrecognized compensation costs, net of estimated forfeitures, related to RSUs granted to employees, which are expected to be recognized over a remaining weighted average period of 1.8 years. The total fair value of the RSUs that vested during the year ended December 31, 2018 was $3.4 million.

In connection with RSUs granted to consultants, the Company recognized a de minimis amount in share-based compensation expense during the year ended December 31, 2018, net of expected forfeitures. In connection with RSUs granted to consultants, the Company recognized approximately $0.3 million in share-based compensation expense during the year ended December 31, 2017. As of December 31, 2018, there were approximately $0.1 million of unrecognized compensation costs, net of estimated forfeitures, related to RSUs granted to consultants, which are expected to be recognized over a remaining weighted average period of 1.0 years.

In connection with the ESPP made available to employees, the Company recognized a de minimis amount and $0.1 million of share-based compensation expense during the years ended December 31, 2018 and December 31, 2017, respectively,

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

12. Stock Option and Compensation Plans (Continued)

net of expected forfeitures. As of December 31, 2018, there was a de minimis amount of unrecognized compensation costs, net of estimated forfeitures, related to the ESPP, which are expected to be recognized over 0.3 years. There were 31,413 shares of common stock issued under the ESPP during the year ended December 31, 2018. Cash proceeds from ESPP purchases were $65 thousand during the year ended December 31, 2018. There were 16,358 shares of common stock issued under the ESPP during the year ended December 31, 2017. As of December 31, 2018, 952,229 shares were available for future purchases under the ESPP.

13. Employee Benefit Plan

The Company maintains a defined contribution 401(k) plan available to employees. Employee contributions are voluntary and are determined on an individual basis, limited by the maximum amounts allowable under federal tax regulations. The Company's matching contributions to employees totaled approximately $0.2 million, $0.7 million and $0.8 million during the years ended December 31, 2018, 2017 and 2016, respectively.

14. Restructuring Activities

In December 2016, the Company announced its intention to implement a reduction in personnel to focus on an updated business plan. In January 2017, the board of directors approved a plan to implement a reduction in personnel involving approximately 80% of the Company's workforce based on the number of employees at the time the plan was approved. The reduction in personnel was substantially completed during 2017 with a limited number of departing employees receiving severance payments during 2018.

As of December 31, 2018, the Company had completed its reduction in personnel and the payment of its remaining accrued severance and other employee costs. The following is a reconciliation of the severance-related accrual activity for the year ended December 31, 2018:

	Accrued Severance and Other Employee Costs
Beginning Balance	$ 2,529
Accrued restructuring expenses	—
Payments	(2,529)
Ending Balance	$ —

15. Selected Quarterly Financial Information (unaudited)

The following is a summary of the quarterly results of operations for the years ended December 31, 2018 and 2017:

	2018			
	March 31	June 30	September 30	December 31
Collaboration revenue	$ —	$ —	$ —	$ —
Research and development expenses	7,686	8,516	9,407	16,128
General and administrative expenses	5,645	6,332	5,968	5,667
Loss from operations	(13,331)	(14,848)	(15,375)	(21,795)
Net income (loss) attributable to common stockholders	$ (13,073)	$ (13,209)	$ (14,745)	$ 104,114
Basic earnings (loss) per common share	$ (0.36)	$ (0.37)	$ (0.41)	$ 2.62
Diluted earnings (loss) per common share	$ (0.36)	$ (0.37)	$ (0.41)	$ 2.62

OPHTHOTECH CORPORATION

Notes to Financial Statements (Continued)

(tabular dollars and shares in thousands, except per share data)

15. Selected Quarterly Financial Information (unaudited) (Continued)

	2017			
	March 31	June 30	September 30	December 31
Collaboration revenue	$ 1,662	$ 1,661	$ 206,654	$ —
Research and development expenses	31,979	15,657	10,707	7,946
General and administrative expenses	13,159	8,552	7,059	6,913
Income (loss) from operations	(43,476)	(22,548)	188,888	(14,859)
Net income (loss) attributable to common stockholders	$ (43,122)	$ (22,204)	$ 189,073	$ (9,542)
Basic earnings (loss) per common share	$ (1.20)	$ (0.62)	$ 5.26	$ (0.26)
Diluted earnings (loss) per common share	$ (1.20)	$ (0.62)	$ 5.25	$ (0.26)

Exhibit 21.1

Subsidiaries of Ophthotech Corporation
as of December 31, 2018

Orion Ophthalmology LLC, a Delaware limited liability company, United States

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statement (Form S-3 No. 333-226497) of Ophthotech Corporation effective August 15, 2018,

(2) Registration Statement (Form S-8 No. 333-223537) pertaining to the 2013 Stock Incentive Plan of Ophthotech Corporation effective March 9, 2018,

(3) Registration Statement (Form S-8 No. 333-219656) pertaining to the 2013 Stock Incentive Plan of Ophthotech Corporation effective August 3, 2017,

(4) Registration Statement (Form S-8 No. 333-211916) pertaining to the 2016 Employee Stock Purchase Plan of Ophthotech Corporation effective June 8, 2016,

(5) Registration Statement (Form S-8 No. 333-208893) pertaining to the 2013 Stock Incentive Plan and inducement stock option grants of Ophthotech Corporation, effective January 6, 2016,

(6) Registration Statement (Form S-8 No. 333-202438) pertaining to the 2013 Stock Incentive Plan and inducement stock option grants of Ophthotech Corporation, effective March 2, 2015,

(7) Registration Statement (Form S-8 No. 333-193694) pertaining to the 2013 Stock Incentive Plan of Ophthotech Corporation, effective January 31, 2014,

(8) Registration Statement (Form S-8 No. 333-191767) pertaining to the 2013 Stock Incentive Plan and Amended and Restated 2007 Stock Incentive Plan, as amended, of Ophthotech Corporation, effective October 16, 2013,

of our reports dated February 28, 2019, with respect to the consolidated financial statements of Ophthotech Corporation, and the effectiveness of internal control over financial reporting of Ophthotech Corporation included in this Annual Report (Form 10-K) of Ophthotech Corporation for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Iselin, New Jersey

February 28, 2019

Exhibit 31.1

CERTIFICATIONS

I, Glenn P. Sblendorio, certify that:

1. I have reviewed this Annual Report on Form 10-K for the fiscal year ended December 31, 2018 of Ophthotech Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 28, 2019

By: /s/ Glenn P. Sblendorio

Glenn P. Sblendorio
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, David F. Carroll, certify that:

1. I have reviewed this Annual Report on Form 10-K for the fiscal year ended December 31, 2018 of Ophthotech Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 28, 2019

By: /s/ David F. Carroll

David F. Carroll
Chief Financial Officer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Ophthotech Corporation (the "Company") for the fiscal year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Glenn P. Sblendorio, Chief Executive Officer of the Company, hereby certifies, pursuant to Rule 13a-14(b) and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 28, 2019

By: /s/ Glenn P. Sblendorio

Glenn P. Sblendorio
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Ophthotech Corporation (the "Company") for the fiscal year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, David F. Carroll, Chief Financial Officer of the Company, hereby certifies, pursuant to Rule 13a-14(b) and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 28, 2019

By: /s/ David F. Carroll

David F. Carroll
Chief Financial Officer
(Principal Financial Officer)