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, 2019

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

IVERIC bio, Inc.
(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	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value	ISEE	The Nasdaq Global Select Market

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

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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, 2019, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $51.6 million, based on the closing price of the registrant's common stock on June 28, 2019.

The number of shares outstanding of the registrant's class of common stock, as of February 24, 2020: 49,688,230

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report incorporates by reference information from the definitive Proxy Statement for the registrant's 2020 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, 2019.

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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 our therapeutic and gene therapy product candidates and programs and pursue our collaborative gene therapy sponsored research programs;
- our expectations regarding the impact of results from our OPH2003 pivotal clinical trial evaluating Zimura for the treatment of geographic atrophy secondary to dry age-related macular degeneration on our business strategy, including our plans to pursue further development of Zimura and/or seek potential collaboration or outlicensing opportunities;
- the timing, costs, conduct and outcome of ISEE2008, our planned Phase 3 clinical trial evaluating Zimura for the treatment of geographic atrophy secondary to dry age-related macular degeneration, and expectations regarding the potential for Zimura to receive regulatory approval for the treatment of geographic atrophy secondary to dry age-related macular degeneration based on the clinical trial results we have received to date and future results from the ISEE2008 clinical trial and any other trials we may conduct;
- the potential advantages of our product candidates and other technologies that we are pursuing, including the advantages and limitations of inhibition of complement factor C5 and HtrA1, including our hypotheses regarding complement inhibition as a mechanism of action to treat geographic atrophy, and of gene therapy, including the use of minigenes;
- our estimates regarding the number of patients affected by the diseases our product candidates and development programs are intended to treat;
- the timing, costs, conduct and outcome of our ongoing and planned clinical trials, including statements regarding the timing of the initiation and completion of, and the receipt of results from, such clinical trials, the costs to conduct such clinical trials, and the impact of the results of such clinical trials on our business strategy;
- the timing, costs, conduct and outcome of our ongoing and planned research and preclinical development activities, including statements regarding the timing of the initiation and completion of, and the receipt of results from, such activities, the costs to conduct such activities, and the impact of the results of such activities on our business strategy;
- our ability to establish and maintain arrangements and capabilities for the manufacture of our therapeutics and gene therapy product candidates, including scale up and validation of the manufacturing process for Zimura;
- 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 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;
- our ability to consummate business development transactions, including potential collaboration or out-licensing opportunities for further development and potential commercialization of Zimura or in-license or other opportunities to acquire rights to additional product candidates or technologies to treat retinal diseases;
- our estimates regarding the potential market opportunity for our product candidates;

- our sales, marketing and distribution capabilities and strategy;
- the rate and degree of potential market acceptance and clinical utility of our product candidates, if approved;
- the potential receipt of revenues from future sales of our product candidates, if approved;
- 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.

USE OF TRADEMARKS

The trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners. We have omitted the ® and ™ designations, as applicable, for the trademarks named in this Annual Report on Form 10-K after their first reference in this Annual Report on Form 10-K.

PART I

Item 1. Business

Overview and Our Strategy

We are a science-driven biopharmaceutical company focused on the discovery and development of novel treatment options for retinal diseases with significant unmet medical needs. We are currently developing both therapeutic product candidates for age-related retinal diseases and gene therapy product candidates for orphan inherited retinal diseases, or IRDs. In April 2019, we changed our name from Ophthotech Corporation to IVERIC bio, Inc. as we continued to broaden the focus of our company to include gene therapies.

We believe that both therapeutics and gene therapy serve important roles in drug development and providing potential treatment options for patients suffering from retinal diseases. Our most advanced therapeutic product candidate is Zimura® (avacincaptad pegol), a complement C5 inhibitor. In October 2019, we announced initial, top-line data from a randomized, controlled clinical trial of Zimura in geographic atrophy, or GA, secondary to dry age-related macular degeneration, or AMD, which we refer to as the OPH2003 trial. The top-line data confirmed that Zimura met the prespecified primary endpoint in the trial in reducing the rate of GA growth in patients with dry AMD. The reduction in the mean rate of GA growth over 12 months using the square root transformation was 0.110 mm (p-value = 0.0072) for the Zimura 2 mg group as compared to the corresponding sham control group and 0.124 mm (p-value = 0.0051) for the Zimura 4 mg group as compared to the corresponding sham control group, indicating an approximate 27% relative reduction in the mean rate of GA growth over 12 months when compared with sham for both dose groups. These data for both dose groups were statistically significant and we believe demonstrate a clinically relevant reduction in rate of GA growth. Based on our review of the safety data to date, Zimura was generally well tolerated over 12 months of administration in this clinical trial. Over this 12-month period, there were no investigator-reported ocular serious adverse events, no Zimura-related adverse events, no cases of Zimura-related intraocular inflammation, no cases of Zimura-related increased intraocular pressure, no cases of endophthalmitis, and no discontinuations

attributed by investigators to Zimura. OPH2003 was designed to be a Phase 2b screening trial, with the potential to qualify as a pivotal trial depending on the magnitude and statistical significance of the potential benefit observed. We believe that the safety and efficacy results from the OPH2003 trial could potentially satisfy the U.S. Food and Drug Administration's, or FDA's, requirements as one of the two pivotal clinical trials typically required for marketing approval of a pharmaceutical product. We are preparing for an international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial of Zimura in this indication, which we refer to as the ISEE2008 trial, with the goal of beginning patient enrollment during the first quarter of 2020.

We currently have two gene therapy product candidates in preclinical development and several collaborative gene therapy sponsored research programs ongoing. Subject to successful completion of preclinical development and manufacturing under current good manufacturing practices, or GMP, and regulatory review, we plan to initiate a Phase 1/2 clinical trial for IC-100, our lead gene therapy product candidate, during the fourth quarter of 2020.

We believe a number of factors provide us a competitive advantage in retinal drug development for therapeutics and gene therapies. These factors include:

- **Broad and deep portfolio of product candidates.** We have built a broad and deep portfolio of therapeutic and gene therapy product candidates and programs that we believe are scientifically compelling, target diseases for which there are high unmet medical needs, and provide significant market opportunities. For our gene therapies, we are focused on using adeno-associated virus, or AAV, for gene delivery, which we believe holds tremendous promise for treating a number of IRDs for which there are no currently approved treatments.

- **Our clinical experience and growing capabilities.** Our team has significant experience in the efficient execution of large-scale clinical trials for retinal diseases, and we intend to leverage that experience as we continue the clinical development of Zimura and prepare for the potential clinical development of our gene therapy product candidates. We are continuing to build our internal and external capabilities in various areas, such as preclinical research, manufacturing, analytical development, quality assurance and control, and regulatory affairs.

- **Collaborative relationships with clinical trial sites and leading academic institutions.** We have deep relationships with global retina thought leaders and an extensive network of over 250 ophthalmic clinical trial sites worldwide with which we have worked. We have developed collaborative relationships with several leading academic institutions in gene therapy research, including the University of Massachusetts Medical School, or UMMS, the University of Pennsylvania, or Penn, and the University of Florida, or UF.

Our therapeutics portfolio consists of Zimura and our preclinical development program of High temperature requirement A serine peptidase 1 protein, or HtrA1, inhibitors. We are targeting the following diseases with Zimura:

- GA, which is the advanced stage of AMD, and is characterized by marked thinning or atrophy of retinal tissue, leading to irreversible loss of vision; and

- autosomal recessive Stargardt disease, or STGD1, which is characterized by progressive damage to the central portion of the retina, or the macula, and other retinal tissue of young adults, leading to loss of vision.

We are developing our HtrA1 inhibitor program for GA and potentially other age-related retinal diseases.

Our gene therapy portfolio consists of several ongoing research and preclinical development programs that use 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;

- IRDs associated with mutations in the *BEST1* gene, including Best vitelliform macular dystrophy, or Best disease, which is generally characterized by bilateral egg yolk-like lesions in the macula, which, over time, progress to atrophy and loss of vision;

- Leber congenital amaurosis type 10, or LCA10, which is characterized by severe bilateral loss of vision at or soon after birth;

- autosomal recessive Stargardt disease; and

- IRDs associated with mutations in the *USH2A* gene, which include Usher syndrome type 2A, or Usher 2A, and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa.

Research and Development Pipeline

We have summarized the current status of our ongoing research and development programs in the table below. We have given an IC number (IC-100 and IC-200) to our preclinical gene therapy product candidates. In the future, we intend to give an IC number to other product candidates that advance to preclinical development, whether from our collaborative gene therapy sponsored research programs or our HtrA1 inhibitor program or that we may otherwise in-license or acquire, in each case, once a lead product candidate is identified for a particular program.

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

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 and are planning an additional, Phase 3 clinical trial for Zimura. The following is a brief description of these trials and their current status:

- **OPH2003 (GA secondary to dry AMD)**: an ongoing international, randomized, double masked, sham controlled, multi-center pivotal clinical trial evaluating the safety and efficacy of various doses of Zimura in patients with GA secondary to dry AMD. We enrolled a total of 286 patients in this trial. In October 2019, we announced initial, top-line data from this trial based on the first 12 months of this trial. This trial remains ongoing and, in accordance with the clinical trial protocol, patients will continue to be treated and followed through month 18. The primary purpose of the 18 month time point is to gather additional safety data. This trial is not designed to assess, and the prespecified statistical analysis plan for the trial does not include assessing, the statistical significance of the 18 month efficacy data for the treatment groups as compared to the corresponding sham control groups. Any analysis of the 18-month efficacy data will be descriptive only. We expect the month 18 data to be available by the end of the second quarter of 2020.

- **ISEE2008 (GA secondary to dry AMD):** a planned international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial evaluating the safety and efficacy of Zimura 2 mg in patients with GA secondary to dry AMD. The primary efficacy endpoint for this trial will be the same as the primary efficacy endpoint for the OPH2003 trial, and, if data from this trial are positive, we expect this trial to potentially qualify

as a second, pivotal clinical trial that may provide data, together with the data from our other Zimura clinical trials, to support a marketing application for Zimura in GA. We plan to enroll approximately 400 patients in this trial, with the goal of beginning patient enrollment during the first quarter of 2020.

- **OPH2005 (STGD1)**: an ongoing, randomized, double masked, sham controlled, multi-center Phase 2b clinical trial, which we refer to as the OPH2005 trial, evaluating the safety and efficacy of Zimura for the treatment of STGD1. Similar to OPH2003, OPH2005 was designed to be a Phase 2b screening trial, with the potential to demonstrate statistically significant results depending on the magnitude of the potential benefit observed, and which we believe could potentially serve as a pivotal clinical trial. We completed enrollment for this 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 our HtrA1 inhibitor program for the treatment of GA secondary to dry AMD and potentially other age-related retinal diseases. Our HtrA1 inhibitor program includes a number of small molecule compounds that show high affinity and specificity for HtrA1 when tested. We have identified a lead compound from this program. We are pursuing process development and formulation development with the goal of developing a manufacturing process and a formulation for intravitreal administration of this lead compound in the eye. If we are successful in developing a manufacturing process for and formulating this lead compound, we plan to initiate investigational new drug, or IND, enabling activities for this product candidate. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing, we plan to file an IND for a product candidate from this program during 2021.

Gene Therapy Research and Development Programs

IC-100: Product Candidate for RHO-adRP

We are pursuing the preclinical development of IC-100, 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 Penn. We and Penn are conducting preclinical studies of IC-100 and a natural history study of RHO-adRP patients. In parallel, 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 IC-100. We are conducting Phase 1/2 clinical manufacturing and other IND-enabling activities, including toxicology studies. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing and regulatory review, we plan to initiate a Phase 1/2 clinical trial for IC-100 during the fourth quarter of 2020.

IC-200: Product Candidate for BEST1-Related IRDs

We are pursuing the preclinical development of IC-200, our novel AAV gene therapy product candidate for the treatment of *BEST1*-related IRDs, including Best disease, to which we acquired exclusive development and commercialization rights through an April 2019 license agreement with Penn and UFRF. We and Penn are conducting preclinical studies of IC-200 and natural history studies of patients with *BEST1*-related IRDs. In parallel, we have engaged a gene therapy CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of IC-200. We are planning for Phase 1/2 clinical manufacturing and other IND-enabling activities. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing and regulatory review, we expect to initiate a Phase 1/2 clinical trial for IC-200 during the first half of 2021.

Minigene Programs

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 goal of minigene therapy is to deliver a gene expressing a protein that, although different from the naturally occurring protein, is nonetheless functional for purposes of treating the associated disease.

We are funding several sponsored research programs at UMMS seeking to use a minigene approach to develop new gene therapies for several orphan IRDs. The following is a summary of these minigene programs and their status:

- **miniCEP290 (LCA10):** This program, which we refer to as the miniCEP290 program, is targeting LCA10, which is associated with mutations in the *CEP290* gene. In July 2019, we entered into a license agreement with the University of Massachusetts, or UMass, for exclusive development and commercialization rights to this program. The sponsored research, which is ongoing, has yielded a number of minigene constructs that show encouraging results when tested in a mouse model. UMMS is continuing to optimize constructs with the goal of identifying a lead construct by the middle of 2020.

- **miniABCA4 (STGD1):** This program, which we refer to as the miniABCA4 program, is targeting STGD1, which is associated with mutations in the *ABCA4* gene. UMMS has generated and is evaluating several *ABCA4* minigene constructs in both *in vitro* and *in vivo* experiments. We have received preliminary results and expect to receive additional results from the miniABCA4 program during the second half of 2020.

- **miniUSH2A (*USH2A*-related IRDs):** This program, which we refer to as the miniUSH2A program, is targeting IRDs associated with mutations in the *USH2A* gene, including Usher 2A and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa. We initiated this sponsored research with UMMS in July 2019 and expect to receive preliminary results during the second half of 2020.

In addition to the license agreement for the miniCEP290 program, 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.

Business Development and Financing Activities

Since early 2017, we have been pursuing a business development strategy to evaluate available technologies to treat ophthalmic diseases, particularly those in the back of the eye, and to explore opportunities to obtain rights to additional products and product candidates employing these technologies. As we evaluated numerous potential opportunities, we have come to believe that gene therapy, in addition to therapeutics, is a promising treatment modality for retina diseases for which there are significant unmet medical needs. Our efforts have resulted in the expansion of our research and development pipeline, including in 2018 and 2019, the addition of several gene therapy product candidates and collaborative gene therapy sponsored research programs as well as our HtrA1 inhibitor program.

In December 2019, we completed an underwritten public offering in which we sold approximately 7,750,000 shares of our common stock, which includes shares purchased pursuant to the underwriters' option to purchase additional shares of our common stock, at a public offering price of $4.00 per share. We also sold to certain investors pre-funded warrants to purchase 3,750,000 shares of our common stock at a public offering price of $3.999 per share underlying each warrant. We raised approximately $42.6 million in net proceeds from this offering.

As we continue the development of our product candidates and programs and evaluate our overall strategic priorities, we will continue to pursue selective business development and financing opportunities that advance us toward our strategic goals. We have been, and plan to continue, exploring options for the future development and potential commercialization of Zimura, including potential collaboration and out-licensing opportunities, including for indications for which we previously developed Zimura such as wet AMD and idiopathic polypoidal choroidal vasculopathy, or IPCV. In addition, we expect to continue to evaluate, on a selective and targeted basis, opportunities to potentially obtain rights to additional product candidates and technologies for retinal diseases. We could also consider business development opportunities that also offer us a financing opportunity. We will continue to pursue capital raising opportunities when they are available on terms that are favorable to us and if the opportunity advances our strategic goals.

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 an age-related disease characterized by progressive degenerative abnormalities in the macula, a small area in the central portion of the retina responsible for central vision. AMD is characteristically a disease of the elderly and is the leading cause of visual loss in individuals over 50 years of age in developed countries. Based on a 2016 epidemiology paper published in *Eye and Vision*, we estimate that currently approximately 11 million individuals in the United States and 170 million individuals worldwide have a form of AMD. Because of increasing life expectancy in developed and developing countries, the elderly population is expected to grow significantly in coming decades. Projections based on U.S. Census Bureau data suggest that the number of Americans over the age of 65 will more than double to approximately 80 million by the middle of this century. In the absence of adequate prevention or treatment measures, the number of cases of AMD with visual loss is expected to grow in parallel with the aging population, leading to a major public health challenge with significant socioeconomic implications.

AMD, at its early stages, presents with abnormalities in the retinal pigment epithelium, or the RPE, and yellow-white deposits under the RPE known as drusen. 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. As the disease progresses with age to the advanced stage, it generally progresses as either the non-neovascular or dry form of AMD or the neovascular or wet form of the disease. In the dry form of AMD, the eventual loss of photoreceptors, RPE cells and associated capillary blood vessels in the macula results in marked thinning and/or atrophy of retinal tissue. This advanced stage of dry AMD is called GA. In the wet form of AMD, abnormal new blood vessels originate beneath the retina, in a layer called the choroid, and invade into the overlying retinal layers, through a process called choroidal neovascularization, or CNV. The macula of patients diagnosed with the wet form of AMD, who are usually treated with currently approved standard of care anti-vascular endothelial growth factor, or anti-VEGF, therapies, can continue to atrophy resulting in GA, which suggests that in many AMD patients, regardless of whether they have the dry or the wet form, the final anatomic outcome leading to loss of vision is GA.

GA is a significant cause of bilateral, irreversible and severe loss of functional vision. GA has a major impact on the functional vision, quality of life, and independence of affected individuals. The median time for development of central GA from the time of diagnosis is two and a half years with the condition expected to develop in the fellow eye within approximately seven years. Based on a comprehensive epidemiology study published in 2004 in *Archives of Ophthalmology,* we estimate that there are currently approximately 1.5 million people in the United States with GA. Furthermore, based on a study published in 2015 in the *American Journal of Ophthalmology,* we estimate that approximately 159,000 people in the United States develop GA each year. Although anti-VEGF therapy is available for treatment of wet AMD, no FDA or European Medicines Agency, or EMA, approved treatment is currently available for GA.

The absence of treatment options for GA secondary to dry AMD represents an area of urgent unmet medical need and a major public health concern for the expanding elderly population.

Inherited Retinal Diseases

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. The most common form of Stargardt disease is STGD1, the autosomal recessive form. STGD1 is caused by mutations in the *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.

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 the EU5, which consists of France, Germany, Italy, Spain and the United Kingdom, the five major market countries for pharmaceutical treatments in Western Europe, on a combined basis there are currently a total of 62,000 to 77,000 affected persons. 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 *RHO*, the gene that encodes for rhodopsin. The presence of a mutated *RHO* gene is linked to the occurrence of RHO-adRP.

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 RHO-adRP.

BEST1-Related IRDs

The *BEST1* gene encodes for 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 *BEST1*-related IRD is 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 *BEST1*-related IRDs being studied, including autosomal recessive forms.

Based on disease prevalence rates contained in a study published in *Ophthalmic Genetics* in 2017, we estimate that in the United States and EU5 on a combined basis, there are a total of approximately 10,000 to 40,000 affected persons with *BEST1*-related IRDs, the substantial majority of whom we believe have the autosomal dominant form of Best disease. There are currently no FDA or EMA approved therapies to treat any *BEST1*-related IRD.

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.

USH2A-Related IRDs

The *USH2A* gene encodes for a protein called usherin. Usherin is believed to be important in the development and maintenance of cells in the retina and the inner ear. There are two principal IRDs associated with mutations in the *USH2A* gene: Usher 2A and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa. Usher 2A is an autosomal recessive syndrome characterized by hearing loss from birth and progressive vision loss, due to RP, that begins in adolescence or adulthood. *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa is a genetic condition that manifests as vision loss without associated hearing loss.

Based on a study published in *Experimental Eye Research* in 2004, we estimate that in the United States and EU5 on a combined basis, there are a total of approximately 20,000 to 62,000 affected persons with *USH2A*-related IRDs. There are currently no FDA or EMA approved therapies to treat Usher 2A or *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa.

Zimura

We are currently 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.

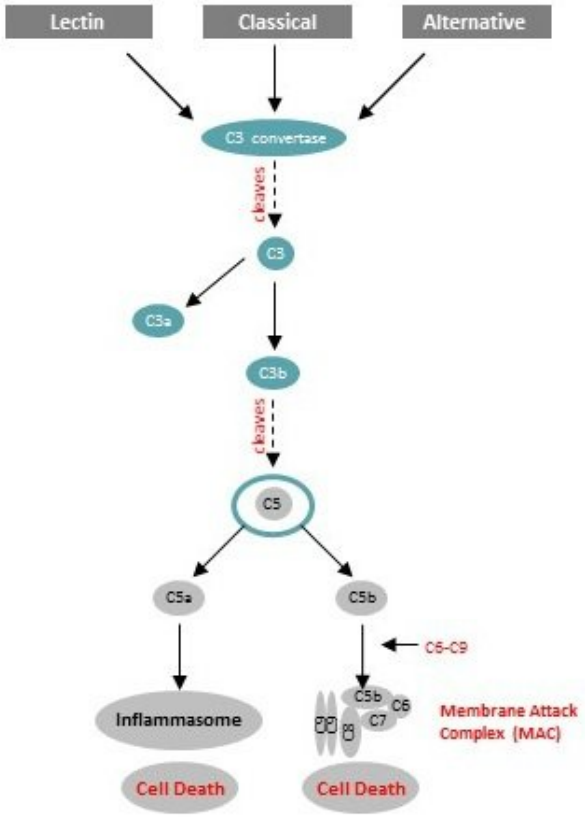
The Complement System and Its Potential Role in GA and STGD1

The complement system consists of a series of proteins that are involved in the defense of the 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 body by removing the pathogens and foreign proteins, along with other cellular debris. The complement system is generally tightly regulated, achieving the proper balance of activation and inhibition depending on the 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 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 system, 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. Other studies have shown the presence of inflammasomes inside the RPE cells of post-mortem eyes of patients with GA. 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. In particular, various studies have shown that MAC, together with the presence of lipofuscin, a yellow-brown waste byproduct from the visual cycle that is commonly found in the RPE cells of AMD patients, interferes with the proper functioning of RPE cells, leading to their dysfunction and 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 leads 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 currently have two clinical trials for Zimura ongoing and are planning an additional, Phase 3 clinical trial for Zimura. The following is a brief description of these trials and their current status:

- **OPH2003 (GA secondary to dry AMD)**: an ongoing international, randomized, double masked, sham controlled, multi-center pivotal clinical trial evaluating the safety and efficacy of various doses of Zimura in patients with GA secondary to dry AMD. We enrolled a total of 286 patients in this trial. In October 2019, we announced initial, top-line data from this trial based on the first 12 months of this trial. This trial remains ongoing and, in accordance with the clinical trial protocol, patients will continue to be treated and followed through month 18. The primary purpose of the 18 month time point is to gather additional safety data. This trial is not designed to assess, and the prespecified statistical analysis plan for the trial does not include assessing, the statistical significance of the 18 month efficacy data for the treatment groups as compared to the corresponding sham control groups. Any analysis of the 18-month efficacy data will be descriptive only. We expect the month 18 data to be available by the end of the second quarter of 2020.

- **ISEE2008 (GA secondary to dry AMD):** a planned international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial evaluating the safety and efficacy of Zimura 2 mg in patients with GA secondary to dry AMD. The primary efficacy endpoint for this trial will be the same as the primary efficacy endpoint for the OPH2003 trial, and we expect this trial to potentially be a second, pivotal clinical trial that may provide data, together with the data from our other Zimura clinical trials, to support a marketing application for Zimura in GA. We plan to enroll approximately 400 patients in this trial, with the goal of beginning patient enrollment during the first quarter of 2020.

- **OPH2005 (STGD1)**: an ongoing, randomized, double masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of Zimura for the treatment of STGD1. Similar to OPH2003, OPH2005 was designed to be a Phase 2b screening trial, with the potential to demonstrate statistically significant results depending on the magnitude of the potential benefit observed, and which we believe could potentially serve as a pivotal clinical trial. We completed enrollment for this 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.

In addition to the above ongoing and planned Zimura clinical trials, 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.

Although we are not currently pursuing further development of Zimura in wet AMD or IPCV, we may evaluate opportunities for further development of Zimura in these indications with a potential collaborator.

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.

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

Zimura - Dry AMD Trials

OPH2003: Ongoing Clinical Trial Assessing the Safety and Efficacy of Various Doses of Zimura for GA Secondary to Dry AMD

In October 2019, we announced initial, top-line data from OPH2003, an international, randomized, double masked, sham controlled, multi-center clinical trial evaluating the safety and efficacy of various doses of Zimura in patients with GA secondary to dry AMD. The primary efficacy analysis was performed at the 12-month time point, and the data we announced in October 2019 was for the first 12 months of the trial. Pursuant to the clinical trial protocol, patients will continue to be treated and followed through month 18 in order to collect additional data regarding Zimura in GA. Throughout the duration of the trial, we have been masked regarding the treatment group to which each individual patient was randomized and expect to remain masked until the patient reaches month 18. The prespecified statistical analysis plan for the trial does not include assessing the statistical significance of the 18 month efficacy data for the treatment groups as compared to the corresponding sham control groups. Any analysis of the month 18 efficacy data will be descriptive only.

Trial Design and Enrollment

A total of 286 patients were enrolled across two parts of the trial.

Part 1. In Part 1 of the trial, 77 patients were randomized into one of three treatment groups in a 1:1:1 ratio as follows:

Cohort	Zimura 1 mg	Zimura 2 mg	Sham
Patients	26	25	26

In Part 1 of the trial, Zimura was administered by monthly intravitreal injections, while patients in the sham control group received monthly sham injections. In 2017, based on the announcement of positive data from a competitor studying a different complement inhibitor in a Phase 2 clinical trial in GA and following review of additional third-party clinical trial data and further statistical analysis, we modified the trial design to change the total number of patients to be enrolled, to change the primary efficacy endpoint from a vision endpoint to an anatomic endpoint, to shorten the time point for the primary efficacy analysis to month 12 and to include a Zimura 4 mg dose group. The patients who were enrolled in Part 1 remained in the trial following these modifications and we remained masked regarding the treatment group to which each patient was randomized.

Part 2. In Part 2 of the trial, we enrolled 209 additional patients, who were randomized into one of three treatment groups in a 1:2:2 ratio as follows:

Cohort	Zimura 2 mg	Zimura 4 mg	Sham
Patients	42	83	84

In Part 2 of the trial, patients in the Zimura 2 mg group received one intravitreal injection of Zimura 2 mg and one sham injection at each monthly visit; patients in the Zimura 4 mg group received two intravitreal injections of Zimura 2 mg at each monthly visit; and patients in the sham control group received two sham injections at each monthly visit. In its current formulation, doses of Zimura above 2 mg would require more than one intravitreal injection.

The primary efficacy endpoint was the mean rate of growth of GA over 12 months, while secondary efficacy endpoints evaluated mean changes in patients' visual acuity in different lighting conditions over the same period.

Key Inclusion and Exclusion Criteria

In order to determine eligibility to participate in the trial, the location and size of each patient's GA was assessed using fundus autofluorescence, or FAF, images. FAF is a common imaging technique used by retina specialists 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 FAF images, areas of atrophy are characterized by lower autofluorescence. An independent masked reading center assessed FAF images throughout the trial, including at baseline to determine eligibility.

The fovea is the central portion of the macula where visual acuity is the highest. We sought to enroll patients whose GA was located, in whole or in part, within 1500 microns of the foveal center but that did not enter the foveal center. A disc area is the size of the area of the retina where a standard sized optic nerve emerges, which is generally accepted to be 2.5 mm^2. We sought to enroll patients with a total GA area of between 1 and 7 disc areas (or 2.5 mm^2 to 17.5 mm^2) inclusive. If the GA was multifocal, meaning it was not continuous and had multiple locations, at least one focal lesion needed to measure at least 0.5 disc areas (or 1.25 mm^2). Each patient's best corrected visual acuity, or BCVA, was also assessed using the Snellen equivalent scale, which equates the detail a patient can see at a distance of 20 feet with the detail an individual with 20/20 vision can see at a greater distance. For example, a patient with 20/50 vision sees at 20 feet what a person with 20/20 vision would see at 50 feet. To be eligible to participate in the trial, patients' BCVA in the study eye was initially required to be between 20/25 and 20/100 inclusive during Part 1 of the trial. As part of the modifications we made for Part 2 of the trial, we expanded the inclusion criteria to include patients whose BCVA in the study eye was between 20/25 and 20/320 inclusive. BCVA on the Snellen equivalent scale can be equated to a number of letters of vision on the Early Treatment of Diabetic Retinopathy Study, or ETDRS, chart. BCVAs of 20/25, 20/100 and 20/320 on the Snellen equivalent scale are equivalent to 80 ETDRS letters, 50 ETDRS letters and 25 ETDRS letters, respectively.

Patients were stratified across treatment groups by baseline BCVA, baseline GA area and the baseline pattern of autofluorescence at the margins of the GA lesion, referred to as the junctional zone. Stratification for baseline characteristics is a method for allocating patients to treatment groups to ensure that there are approximately the same ratio of patients with a given baseline characteristic in each treatment group as the overall randomization ratio. For vision, patients were stratified based on whether their vision was above or below 50 ETDRS letters. For GA area, patients were stratified based on whether their GA area was above or below 4 disc areas. For autofluorescence pattern, patients were stratified based on several well-known patterns that have been described in the scientific literature.

As part of the modifications for Part 2 of the trial, we amended the clinical trial protocol to provide that patients in any arm of the trial who developed CNV in the study eye would be removed from the trial and any future study treatments and assessments, since we did not believe that GA lesions for patients with CNV in the study eye could be reliably measured with FAF images.

Additionally, patients who had a prior history of intravitreal treatment for any indication in either eye were excluded, as well as patients with any ocular condition in the study eye that could affect central vision or otherwise confound assessments.

Baseline Characteristics

We collected baseline characteristics for all patients participating in the trial. GA area was measured based on the area of GA in square millimeters (mm^2). Reported scientific literature indicates that the rate of GA growth may be dependent on the baseline lesion size, with larger GA lesions generally growing faster than smaller lesions, subject to an overall plateau effect as the GA grows to consume almost the entire macula. For this reason, patients were stratified in this trial based on their baseline lesion size. To further mitigate for the impact of baseline lesion size on the growth of GA, a square root transformation was performed. It is reported in the scientific literature and accepted in the field that using the square root of the lesion size for calculating the mean change in size over time mitigates for the impact of the baseline lesion size. We used the square root transformation of GA area, measured in millimeters (mm), to perform the assessment of the primary efficacy endpoint in the OPH2003 trial.

Although GA can be associated with profound and irreversible vision loss, the vision loss that patients experience is not necessarily linearly correlated to the progression of GA. The specific location of the GA within patients' retinas can affect patients' vision differently. In general, patients whose GA expands into the fovea experience vision loss that is disproportionate to the vision loss experienced by patients whose GA does not expand into the fovea. Further, patients with GA may demonstrate good visual acuity but poor functional vision if their GA results in dark spots, referred to as scotomas, in their central visual field. Patients with scotomas may be able to read a vision chart letter-by-letter, especially if their GA has not entered the fovea, but they may have trouble reading a paragraph of text or driving, as these activities of daily living draw upon a field of vision that is broader than a single point of focus. For this reason, and based on our prior interactions with the FDA, we believe the efficacy assessment that is most likely to demonstrate clinical relevance for an investigational product across a heterogeneous GA patient population is reduced rate of growth in GA. If an investigational product can slow the growth of GA, it has the potential to preserve, or slow the loss of, functional vision for patients whose GA is expanding into critical areas of their central visual field, which would be clinically meaningful.

In addition to baseline GA area, it has been reported in the scientific literature that GA that is non-subfoveal, or that has not impacted the foveal center, is positively correlated with a higher rate of GA area progression and growth. We believe that once a GA lesion expands into the fovea, the rate of growth may be slowed. In addition, once GA expands to encompass the central fovea, additional progression can be limited in the central region of the retina, with any continued expansion occurring predominantly in the outer part of the retina.

In addition to measuring the area of GA, we followed patients for changes in their vision (BCVA), as measured both at a standard light level, or luminance, and lower light level, or low luminance (LL BCVA), measured in each case by ETDRS letters. Testing for visual acuity serves as an important safety assessment to assure that the decrease in visual acuity in the Zimura treatment groups was not different from the sham control groups. Because we believe that BCVA is not the optimal assessment to evaluate the impact of GA on patients' functional vision, we included vision in the prespecified statistical analysis as a secondary, and not as a primary, endpoint.

For patients within each treatment group, where a numerical measurement was collected, we calculated the mean and standard deviation, or SD, for each measurement. SD is a statistical measure of the variability of a particular measurement within a patient population. Generally, two-thirds of all patients fall within approximately one SD, plus or minus, of the mean for any particular measurement.

The baseline characteristics are presented below for each treatment group in each Part of the trial. These baseline characteristics include the ITT, or intent-to-treat, population, which includes all patients who were randomized in the trial and who received at least one dose of study drug in the relevant treatment group. Based on these data, we believe that the baseline characteristics were generally balanced across the treatment groups.

	Part 1			Part 2		
Cohort	**Zimura 1 mg** (N = 26)	**Zimura 2 mg** (N = 25)	**Sham** (N = 26)	**Zimura 2 mg** (N = 42)	**Zimura 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Mean age, years (SD)	73.8 (8.0)	77.7 (9.6)	78.1 (8.4)	79.4 (10.7)	79.2 (8.3)	78.2 (9.0)
Female gender, number (%)	15 (57.7%)	18 (72.0%)	18 (69.2%)	27 (64.3%)	58 (69.9%)	61 (72.6%)
Active smokers, number (%)	6 (23.1%)	10 (40.0%)	7 (26.9%)	15 (35.7%)	26 (31.3%)	29 (34.5%)
Caucasian race, number (%)	25 (96.2%)	25 (100%)	25 (96.2%)	42 (100%)	82 (98.8%)	82 (97.6%)
Iris color:						
Light	13 (50.0%)	16 (64.0%)	17 (65.4%)	29 (69.0%)	54 (65.1%)	57 (67.9%)
Medium	7 (26.9%)	6 (24.0%)	7 (26.9%)	9 (21.4%)	22 (26.5%)	21 (25.0%)
Dark	6 (23.1%)	3 (12.0%)	2 (7.7%)	4 (9.5%)	7 (8.4%)	6 (7.1%)
Mean intraocular pressure, mmHg (SD)	15.0 (1.9)	14.6 (2.6)	14.5 (2.8)	14.1 (2.4)	15.2 (2.5)	14.9 (2.5)
Non-subfoveal GA, number (%)	23 (88.5%)	20 (80.0%)	22 (84.6%)	42 (100%)	81 (97.6%)	82 (97.6%)
Mean GA area, mm^2 (SD)	7.37 (4.32)	6.60 (3.35)	7.33 (3.73)	7.77 (4.01)	7.90 (4.18)	7.45 (3.89)
Mean Sq. Root of GA area, mm (SD)	2.591 (0.827)	2.471 (0.717)	2.623 (0.687)	2.705 (0.684)	2.715 (0.732)	2.636 (0.709)
Bilateral GA, number (%)	26 (100%)	25 (100%)	25 (96.2%)	42 (100%)	83 (100%)	83 (98.8%)
Mean BCVA, ETDRS letters (SD)	70.5 (8.0)	71.6 (7.5)	71.3 (7.5)	69.4 (11.3)	69.5 (9.8)	68.3 (11.0)
Mean LL BCVA, ETDRS letters (SD)	38.1 (22.7)	43.0 (19.7)	36.7 (21.2)	33.1 (21.3)	36.8 (20.9)	33.9 (18.8)
Patients with Hyperautofluorscence (%)	25 (96.2%)	25 (100%)	26 (100%)	41 (97.6%)	82 (98.8%)	83 (98.8%)
Height, cm (SD)	168.7 (12.0)	165.9 (8.6)	164.9 (12.1)	164.9 (11.0)	163.7 (10.6)	163.7 (9.3)
Weight, kg (SD)	81.9 (17.8)	75.6 (14.9)	74.7 (15.6)	80.8 (22.3)	76.2 (18.2)	78.4 (17.8)

12-Month Safety Data

Based on our review of the safety data to date, Zimura was generally well tolerated after 12 months of administration. Over this 12-month time period, there were no investigator-reported ocular serious adverse events, no Zimura-related adverse events, no cases of Zimura-related intraocular inflammation, no cases of Zimura-related increased intraocular pressure, no cases of endophthalmitis, and no discontinuations attributed by investigators to Zimura in the trial. The numbers below are based on investigator-reported adverse events occurring up through the month 12 time point for all patients.

The number of patients with one or more serious, systemic, treatment emergent adverse events, or TEAEs, organized by MedDRA system organ class, a standard method of reporting adverse events, are set forth in the table below:

Patients with One or More Serious TEAEs in Any Organ Class

	Part 1			Part 2		
	Zimura 1 mg (N = 26)	**Zimura 2 mg** (N = 25)	**Sham** (N = 26)	**Zimura 2 mg** (N = 42)	**Zimura 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Cardiac disorders	1 (3.8%)	0	0	0	2 (2.4%)	3 (3.6%)
Gastrointestinal disorders	1 (3.8%)	1 (4.0%)	1 (3.8%)	0	2 (2.4%)	6 (7.1%)
General disorders and administration site conditions	0	0	0	1 (2.4%)	0	0
Hepatobiliary disorders	0	1 (4.0%)	1 (3.8%)	0	1 (1.2%)	0
Infections and infestations	0	1 (4.0%)	0	1 (2.4%)	6 (7.2%)	2 (2.4%)
Injury, poisoning and procedural complications	0	1 (4.0%)	0	1 (2.4%)	3 (3.6%)	2 (2.4%)
Metabolism and nutrition disorders	0	0	1 (3.8%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (3.8%)	0	0	0	0	2 (2.4%)
Benign, malignant and unspecified neoplasms (including cysts and polyps)	0	0	0	0	1 (1.2%)	2 (2.4%)
Nervous system disorders	1 (3.8%)	1 (4.0%)	1 (3.8%)	1 (2.4%)	3 (3.6%)	1 (1.2%)
Psychiatric disorders	0	0	1 (3.8%)	0	0	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	0	1 (4.0%)	0	0	2 (2.4%)	3 (3.6%)

The number of patients with one or more systemic TEAEs, including serious systemic TEAEs, identified by the investigator as related to the study drug (Zimura or sham) are set forth in the table below:

Reported Systemic TEAEs Related to Zimura or Sham

	Part 1			Part 2		
	Zimura 1 mg (N = 26)	**Zimura 2 mg** (N = 25)	**Sham** (N = 26)	**Zimura 2 mg** (N = 42)	**Zimura 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Subjects with at least one TEAE	0	0	0	0	0	0

The number of patients with one or more ocular TEAEs in the study eye are set forth in the table below:

Reported Ocular TEAEs in Study Eyes

	Part 1			Part 2		
	Zimura 1 mg (N = 26)	**Zimura 2 mg** (N = 25)	**Sham** (N = 26)	**Zimura 2 mg** (N = 42)	**Zimura 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Eye disorders	12 (46.2%)	8 (32.0%)	4 (15.4%)	24 (57.1%)	50 (60.2%)	33 (39.3%)
Eye disorders related to injection procedure	3 (11.5%)	4 (16.0%)	2 (7.7%)	14 (33.3%)	36 (43.4%)	23 (27.4%)

All of the above TEAEs that were not related to the injection procedure were also not related to the study drug. The number of patients with one or more ocular TEAEs in the study eye, identified by the investigator as related to the study drug (Zimura or sham) is set forth in the table below:

Reported Ocular TEAEs in the Study Eye Related to Zimura or Sham

	Part 1			Part 2		
	Zimura 1 mg (N = 26)	**Zimura 2 mg** (N = 25)	**Sham** (N = 26)	**Zimura 2 mg** (N = 42)	**Zimura 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Subjects with at least one TEAE	0	0	0	0	0	0

Incidence of CNV. During the first 12 months of this trial, the incidence of investigator reported CNV in the untreated fellow eyes was 10 patients (3.5%) and in the study eyes was 3 patients (2.7%) in the sham group, 1 patient (4.0%) in the Zimura 1 mg group, 6 patients (9.0%) in the Zimura 2 mg group, and 8 patients (9.6%) in the Zimura 4 mg group.

Statistical Analysis for Efficacy Measures

OPH2003 was designed as a Phase 2b screening trial based on the criteria described by Drs. Thomas Fleming and Barbara Richardson in their publication regarding clinical trial design in the context of microbicides for the prevention of HIV in the *Journal of Infectious Disease* in 2004. A screening trial uses the same primary efficacy endpoint as an anticipated Phase 3 clinical trial that would be used to support potential marketing approval. However, screening trials generally have a considerably smaller sample size than the anticipated Phase 3 clinical trial. Because it is particularly important to avoid false negative outcomes in a screening trial, screening trials may have higher false positive error rates than would typically be allowed in a Phase 3 trial.

A Phase 2b screening trial has three possible outcomes:

- If the estimated effect size indicates low levels of benefit, the experimental intervention would be judged as not plausibly more efficacious than the sham control, and should be discarded in its current dosage in the indication evaluated;
- If the estimated effect size is moderate but clinically relevant, with a relatively low likelihood of being achieved (for example, a probability of less than 10%) if there truly were no effect, the experimental intervention would be judged as plausibly more efficacious than the sham control and should be evaluated definitively in subsequent Phase 3 clinical trials; or
- If the estimated effect size is clinically relevant and reaches the traditional threshold for statistical significance, as was the case in the OPH2003 trial for both the Zimura 2 mg and Zimura 4 mg dose groups as compared to the corresponding sham control groups, the trial could potentially serve as one of the two pivotal trials typically required for marketing approval.

A properly designed Phase 2b screening trial has a considerable likelihood of ruling out ineffective or harmful interventions, while providing encouraging (or even statistically significant) evidence of benefit that likely would require confirmation by one additional, independent Phase 3 trial.

For the primary and secondary efficacy analyses , we evaluated the ITT population in accordance with a prespecified statistical analysis plan.

The statistical evidence from the OPH2003 trial regarding the comparison of Zimura 2 mg to sham control is provided by data from both Part 1, with a 1:1 randomization ratio of patients receiving Zimura 2 mg (25 patients) and sham (26 patients), as well as data from Part 2, with a 1:2 randomization ratio of patients receiving Zimura 2 mg (42 patients) and sham (84 patients), for a total of 67 patients receiving Zimura 2 mg and 110 patients receiving sham. While we believe it is appropriate to use the aggregate data from Parts 1 and 2 in the analysis of the relative effects of Zimura 2 mg as compared to sham, it would not be appropriate to simply pool the data from patients in both Parts 1 and 2, in particular, because the randomization fraction differs across these two parts of the trial. However, based on the randomization procedures used in each part of the trial, for purposes of statistical comparisons, within Part 1 of the trial, the 25 patients receiving Zimura 2 mg should be comparable to the 26 patients receiving sham. Similarly, for purposes of statistical comparisons, within Part 2 of the trial, the 42 patients receiving Zimura 2 mg should be comparable to the 84 patients receiving sham. The efficacy of Zimura 2 mg was therefore evaluated through an analysis which included a regression factor by trial part. The statistical analysis for the Zimura 4 mg group as compared to sham compares data for patients from Part 2 of the trial only. Data from patients receiving Zimura 1 mg in Part 1 of the trial was not part of the prespecified statistical analysis for the efficacy endpoints.

The prespecified statistical analysis plan for the primary and secondary endpoints of this trial used the mixed-effects repeated measures model, or MRM, to compare data for the Zimura 2 mg and Zimura 4 mg groups to the corresponding sham groups. Repeated measures models are often used when the same outcome is measured at several time points for each patient. These models make use of all available data points to estimate the measurement of interest, the mean rate of change of GA growth, without making overly restrictive assumptions. In addition, these models are generally robust to missing data under the assumption that data are missing at random. During the course of a clinical trial, patients may withdraw from the clinical trial because their condition is asymptomatic, because patients believe that continued participation in the trial is not justified based on the time commitment or treatment burden, such as receiving monthly intravitreal injections, at the recommendation of the investigator or because the protocol requires it. Additionally, patients may not come to a scheduled visit at which key assessments are scheduled to be taken or patient data may not be evaluable because of poor image quality or data recording errors. Early withdrawal, missed visits and unevaluable data all result in data missing from the final data set for a clinical trial.

Although the protocol called for collection of FAF images of GA at baseline, at month 6 and at month 12, for patients who withdrew from the trial before month 12, the study protocol required the collection of an FAF image to provide a measurement of GA at the time of withdrawal, which was included in the primary analysis so long as it was taken within the month prior to either the month 6 or month 12 time point. Because the MRM model would only need measurements from at least two different time points for analysis purposes, one of which must be the baseline, we were able to include in the primary analysis all patients who had GA measurements at baseline and within the month prior to either month 6 or month 12, or both.

The following table sets forth for the data in the primary statistical analysis the number of patients for whom GA measurements were missing for purposes of performing this analysis. Patients whose GA measurements were missing at baseline, or at both month 6 and month 12, could not be included in the primary analysis. All other patients were included in the primary analysis.

Cohort	Zimura 2 mg (N = 67)	Sham 2 mg (N = 110)	Zimura 4 mg (N = 83)	Sham 4 mg (N = 84)
Missing GA measurement at BL, M6 and M12	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing GA measurement at M6 and M12 only	8 (11.9%)	11 (10.0%)	17 (20.5%)	5 (6.0%)
Missing GA measurement at BL only	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)
Total patients excluded from MRM analysis	8 (11.9%)	11 (10%)	18 (21.7%)	5 (6.0%)
Missing GA measurement at M6 only	1 (1.5%)	7 (6.4%)	3 (3.6%)	6 (7.1%)
Missing GA measurement at M12 only	10 (14.9%)	9 (8.1%)	11 (13.3%)	7 (8.3%)
No missing GA measurements[(a)]	48 (71.6%)	83 (75.5%)	51 (61.5%)	66 (78.6%)
Total patients included in MRM analysis	59 (88.0%)	99 (90.0%)	65 (78.3%)	79 (94.1%)

BL = Baseline; M6 = Month 6; M12 = Month 12
(a) = complete observations

In total, 53 (18.5%) patients withdrew from the trial during the first 12 months. Of the patients who withdrew during the first 12 months, 2 patients were from the Zimura 1 mg group (7.7% withdrawals), 12 patients were from the combined Zimura 2 mg group (17.9% withdrawals), 25 patients were from the Zimura 4 mg group (30.1% withdrawals) and 14 patients were from the combined sham group (12.7% withdrawals). GA measurements for patients who withdrew from the study prior to the 12 month time point may have been included in the MRM analysis, as detailed in the table above.

Sensitivity analyses. We performed several sensitivity analyses to assess the impact of missing data on the robustness of the OPH2003 trial results. The analyses we performed were based on approaches that the FDA generally recommends sponsors of investigational products use to evaluate their clinical data. Based on these analyses, and accounting for the data missing from our data set because of patient withdrawals or for other reasons, the statistical analysis for the 12 month data from the OPH2003 trial appear to be robust. Descriptions of these sensitivity analyses and their outcomes are summarized below. For a description of the thresholds we used to determine statistical significance on the primary efficacy endpoint, see the paragraph below the tables below under "Primary Efficacy Endpoint Data."

- A "shift imputation" approach, in which missing data are imputed, or replaced, by values calculated from similar patients with observed values, plus a defined shift. The analysis is repeated assuming a progressively larger shift with each iteration. The analysis becomes increasingly conservative as the shift increases (because missing values are replaced by worse values than would have been observed, had the values not been missing). The shift is increased until a tipping point is reached and statistical significance is lost. If significance is lost for smaller shift values, the results of the analyses are sensitive to missing data, whereas if significance is lost for larger shift values, the results of the analyses are robust to missing data.

  A shift of at least 0.05 mm in terms of square root of GA growth was required to lose statistical significance for both the Zimura 2 mg and Zimura 4 mg groups. The difference between the Zimura treatment groups and the corresponding sham groups, in terms of mean change of square root of GA growth, was 0.11 mm for the Zimura 2 mg group and 0.12 mm for the Zimura 4 mg group, so a shift of 0.05 mm represents more than 40% of the observed treatment effect, which is large.

- Arbitrary imputation approaches, in which missing data are replaced by:

  - the mean value of the same treatment group, which seems a reasonable imputation approach since it replaces missing values by the mean of all observed values in the same treatment group;

- the mean value of the comparator treatment group, which is a very conservative approach. If there is a treatment effect, missing values in the sham control group are replaced by better values, on average, from the Zimura treatment group, while missing values in the Zimura treatment group are replaced by worse values, on average, from the sham control group;
- the mean value of both treatment groups, which is a conservative approach because it assumes no treatment effect for missing values; and
- the mean value of the sham control group, which is also a conservative approach because it draws only upon data from the sham control group, which by definition did not have any treatment benefit.

Statistical significance for the reduction in mean rate of GA growth for the Zimura 2 mg and Zimura 4 mg groups as compared to the corresponding sham groups was retained for all arbitrary imputation approaches.

- A "pattern mixture model imputation" approach, which is a technically complex model and is especially useful when data are suspected to be missing "not at random".

  Statistical significance for the reduction in mean rate of GA growth for the Zimura 2 mg and Zimura 4 mg groups as compared to the corresponding sham groups was retained for the pattern mixture model imputation approach, which suggests again that the results of the analyses are robust to missing data, even if these data had been missing not at random.

Based on our sensitivity analyses, and accounting for the data missing from our data set because of patient withdrawals or for other reasons, we believe the statistical analysis for the 12 month data from the OPH2003 trial is robust.

Primary Efficacy Endpoint Data

The prespecified primary efficacy endpoint was an anatomic endpoint, the mean change in rate of GA growth over 12 months, as measured by FAF based on readings at three time points: baseline, month 6 and month 12, calculated using the square root transformation of the GA area. The readings were performed by an independent masked reading center. The primary efficacy endpoint data are summarized in the following table:

Mean Rate of Change in GA Area from Baseline to Month 12
(MRM Analysis) (Square Root Transformation)

Cohort	Zimura 2 mg (N = 67)	Sham 2 mg (N = 110)	**Difference**	**P-value**	**% Difference**
Mean Change in GA[(a)] (mm)	0.292[(b)]	0.402[(b)]	0.110	0.0072[(c)]	27.38%

Cohort	Zimura 4 mg (N = 83)	Sham 4 mg (N = 84)	**Difference**	**P-value**	**% Difference**
Mean Change in GA[(a)] (mm)	0.321	0.444	0.124	0.0051[(c)]	27.81%

(a) = based on the least squares mean from the MRM model.
(b) = these least squares means are estimates from the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data.
(c) = reflects statistically significant p-value; Hochberg procedure was used for significance testing.

The analysis of the mean change in GA growth for Zimura 2 mg as compared to Sham 2 mg was adjusted for the fact that this dose of Zimura was tested in the two parts of the trial, which had different randomization ratios. The least squares mean changes in GA in Part 1 and Part 2 are shown separately in the following table:

Mean Rate of Change in GA Area from Baseline to Month 12
(MRM Analysis) (Square Root Transformation)

Cohort		Zimura 2 mg (N = 25)	Sham 2 mg (N = 26)	**Difference**
Part 1	Mean Change in GA[(a)] (mm)	0.329	0.42249	0.093

(a) = based on the least squares mean from the MRM model

Cohort		Zimura 2 mg (N = 42)	Sham 2 mg (N = 84)	**Difference**
Part 2	Mean Change in GA[(a)] (mm)	0.308	0.42245	0.114

(a) = based on the least squares means from the MRM model

When the data from the Zimura 2 mg comparisons from each Part of the trial are analyzed using the MRM model, which includes a regression factor by part, the mean difference in GA growth over 12 months between the Zimura 2 mg and sham control groups is 0.110 mm.

Statistical significance is established by performing statistical analysis on a data set to assess the degree to which an observed outcome is likely to be associated with variability in the studied patient population or chance as compared to the impact of the investigational product being studied. A higher degree of statistical significance is associated with a lower p-value. Typically, a two-sided p-value of 0.05 or less represents statistical significance when performing only a single prespecified primary analysis for a single primary endpoint. However, when multiple doses of a drug are tested, a more stringent statistical method that accounts for multiple comparisons must be applied. For this purpose, we used the Hochberg multiple comparison procedure to assess the statistical significance of the results observed in the OPH2003 trial. Under the Hochberg procedure, it is necessary to use a stricter standard for statistical significance (a two-sided p-value of 0.025 or less) for any particular dose. For OPH2003, the results for the primary efficacy endpoint observed for both the Zimura 2 mg and Zimura 4 mg groups, as compared to the corresponding sham group, achieved p-values of 0.0072 and 0.0051, respectively, both of which are less than 0.025, indicating that both results were statistically significant.

Secondary Efficacy Endpoints Data

The prespecified secondary endpoints in this trial were the mean change in BCVA from baseline to month 12 and the mean change in LL BCVA from baseline to month 12, both as measured by ETDRS letters. Testing for visual acuity serves as an important safety assessment to assure that the decrease in visual acuity in the Zimura treatment groups was not different from the sham control groups. Because we believe that BCVA is not the optimal assessment to evaluate the impact of GA on patients' functional vision, we included vision in the prespecified statistical analysis as a secondary, and not as a primary, endpoint.

The OPH2003 trial was not designed to reliably assess differences in mean changes in BCVA or LL BCVA with statistical significance. Data for the secondary endpoints are summarized in the following tables:

Mean Change in BCVA from Baseline to Month 12
(MRM Analysis) (ETDRS letters)

Cohort	Zimura 2 mg (N = 67)	Sham 2 mg (N = 110)	**Difference**
Mean Change in BCVA[(a)]	-7.90[(b)]	-9.29[(b)]	1.39

Cohort	Zimura 4 mg (N = 83)	Sham 4 mg (N = 84)	**Difference**
Mean Change in BCVA[(a)]	-3.79	-3.51	-0.28

(a) = based on the least squares mean from the MRM model
(b) = these least squares means are estimates from the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data.

Mean Change in LL BCVA from Baseline to Month 12
(MRM Analysis) (ETDRS letters)

Cohort	Zimura 2 mg (N = 67)	Sham 2 mg (N = 110)	Difference
Mean Change in LL BCVA[(a)]	-1.03[(b)]	-1.41[(b)]	0.38

Cohort	Zimura 4 mg (N = 83)	Sham 4 mg (N = 84)	Difference
Mean Change in LL BCVA[(a)]	1.53	2.97	-1.44

(a) = based on the least squares mean from the MRM model
(b) = these least squares means are estimates from the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data.

Zimura 1 mg 12-Month Efficacy Data

Efficacy data from patients receiving Zimura 1 mg was not part of the prespecified statistical analysis. The total number of patients randomized to the Zimura 1 mg group (26 patients) is relatively small, and the trial was not powered to reliably assess differences in outcomes for these patients as compared to patients in the sham control group in Part 1 (26 patients). However, we performed descriptive analyses on the 12 month data for patients in the Zimura 1 mg as compared to the patients in the sham control group in Part 1 of the trial to aid our assessment of whether a dose response relationship was present across treatment groups included in the clinical trial.

GA area data for the Zimura 1 mg group and the sham group from Part 1 of the trial are summarized in the following tables:

Summary of GA Area (mm) and Mean Percentage Change from Baseline to Month 12
(Square Root Transformation)

Cohort	Zimura 1 mg (N = 26)	Sham Part 1 (N = 26)
Mean Sq. Root of GA at BL, mm (SD)	2.591 (0.827)	2.623 (0.687)
Mean Sq. Root of GA at M12, mm (SD)	3.055 (0.604)	3.021 (0.722)
Difference	0.464	0.398
Mean % Change[(a)] (SD)	14.48% (8.2%)	16.49% (7.2%)

BL = Baseline; M12 = Month 12
(a) Mean % Change in GA area is an average of the percentage change in GA area observed for each patient.

Although the sample size for the Zimura 1 mg group is small, we believe the apparent reduction in mean percentage change in GA area from baseline to month 12 in the Zimura 1 mg group as compared to the sham control group in Part 1, when combined with the statistically significant results observed for the primary efficacy endpoint for the Zimura 2 mg and Zimura 4 mg groups as compared to their corresponding sham control groups, suggest a potential dose response relationship across treatment groups.

Anticipated 18-Month Data

In accordance with the clinical trial protocol, we will continue to treat and follow patients over 18 months to collect additional data for Zimura in GA. Once all patients reach the 18 month time point, we expect that we will receive unmasked individual patient data for all evaluations performed throughout the trial, and, for each treatment group, mean change in the GA lesion area over 18 months, based on the MRM model, and mean BCVA and mean LL BCVA at month 18. The primary purpose of the 18 month time point is to gather additional safety data. This trial is not designed to assess, and the prespecified statistical analysis plan for the trial does not include assessing, the statistical significance of the 18 month efficacy data for the treatment groups as compared to the corresponding sham control groups. Any analysis of the 18-month efficacy data will be descriptive only. We expect the month 18 data to be available by the end of the second quarter of 2020.

Requirements for Regulatory Approval of Zimura in GA

To obtain regulatory approval for Zimura for the treatment of GA secondary to dry AMD, we expect that we will need to obtain favorable results from a total of two independent, adequate and well-controlled pivotal clinical trials, demonstrating the safety and efficacy of Zimura in this indication. To establish efficacy, we believe it would be sufficient to demonstrate

robust, statistically significant results showing a clinically relevant reduction in the rate of growth of GA over 12 months, based on measurements over three time points (baseline, month 6 and month 12) in two independent trials. We selected this measure as the primary endpoint for the OPH2003 trial based on prior formal interactions with the FDA, as well as our understanding of clinical trials for other investigational products in development for the treatment of GA. We designed the OPH2003 trial as a well-controlled screening trial such that, in the event that the prespecified primary efficacy endpoint results were statistically significant, the trial could potentially serve as one of the two pivotal clinical trials typically required for marketing approval. Based on the results we have received, the statistical analysis that we have performed and informal discussions we have had with the FDA, we believe that the safety and efficacy results from our OPH2003 trial could potentially satisfy the FDA's requirements as one of the two pivotal clinical trials typically required for marketing approval. In the paragraphs that follow, we describe in detail the basis for our belief.

Requirements for Safety Data

Zimura has generally been well tolerated in our clinical trials to date. Over the 12-month time point for all patients in the OPH2003 trial, there were no investigator reported ocular serious adverse events, Zimura-related adverse events, cases of Zimura-related intraocular inflammation, cases of Zimura-related increased intraocular pressure, cases of endophthalmitis, or discontinuations attributed by investigators to Zimura in the trial. We believe the investigator reported CNV rate in the study eye for patients receiving Zimura as compared to sham and the untreated fellow eyes during the first 12 months of the trial is within an acceptable range when compared to published clinical trial data for another complement inhibitor currently in development for GA. The most frequently reported ocular adverse events in the OPH2003 trial were related to the injection procedure.

To demonstrate the safety of Zimura to a degree sufficient to support marketing approval, we believe that the FDA and EMA would require data from a minimum of 300 patients having received the dose of Zimura for which we are seeking approval, or a higher Zimura dose, independent of indication, for a minimum of 12 months, with 24-month safety data available for some portion, but not all, of these 300 patients. Including patients randomized to the Zimura 4 mg group in the OPH2005 trial of Zimura for STDG1, we believe that we currently have 12-month safety data for approximately 140 patients who have received either monthly Zimura 2 mg or Zimura 4 mg for 12 months or more. Based on the safety profile of Zimura observed to date in these patients and the number of patients treated, we believe that the remaining minimum safety requirements could potentially be satisfied through a single additional, pivotal clinical trial providing for monthly administrations of Zimura 2 mg over 12 months, at which point the primary efficacy analysis would be performed, with treatment extending to 24 months for the overall safety analysis, with the potential for less frequent dosing after month 12.

Requirements for Efficacy Data

As described above, we believe that reduction in the rate of GA growth over 12 months, based on measurements over three time points (baseline, month 6 and month 12) is an efficacy endpoint that the FDA and EMA would likely accept in considering Zimura for approval for the treatment of GA secondary to dry AMD. The measurements for this endpoint are performed by a masked independent reading center to minimize the potential for bias.

Statistical Significance. In our OPH2003 trial, the reduction in the mean rate of GA growth over 12 months using the square root transformation was 0.110 mm (p-value = 0.0072) for the Zimura 2 mg group as compared to the corresponding sham control group and 0.124 mm (p-value = 0.0051) for the Zimura 4 mg group as compared to the corresponding sham control group, corresponding to an approximate 27% relative reduction in the mean rate of GA growth over 12 months when compared with sham. These data for both dose groups were statistically significant. See above under "Primary Efficacy Endpoint Data" for a discussion of the procedures we used to confirm the statistical significance of these data.

Clinical Relevance. Clinical relevance refers to an assessment of how meaningful the observed outcome is or would be for patients. The FDA and other regulatory authorities consult with clinicians in the field of study to advise on the relevance of an observed outcome for patients. Although there are no FDA or EMA approved therapies for the treatment of GA secondary to dry AMD, we understand that based on recent FDA guidance on human gene therapy products for retinal disorders, the FDA considers best curve fit analyses, such as an MRM model, that demonstrates a statistically significant reduction in the rate of photoreceptor loss, as determined based on FAF images, in a manner that includes measurements at baseline, month 6 and month 12, to be clinically meaningful. Our MRM uses a straight line analysis, which we believe satisfies the FDA's requirement for a best curve fit analysis. We also believe that our anatomic endpoint, reduction in the mean rate of GA growth, is an endpoint that the FDA would consider as a clinically relevant indicator of a reduced rate of photoreceptor loss. Since established literature and clinical experience indicates that patients' functional vision is impacted by the growth of the GA over time, which ultimately leads to severe vision loss, we believe that reduction of GA growth would have a meaningful impact on the patients' well-being and quality of life and therefore is clinically relevant.

To secure approval to market an investigational product, a sponsor must demonstrate to the applicable regulatory authority that the potential benefits to be conferred to patients outweigh the potential risks associated with a treatment.

Robustness. In addition to statistical significance and clinical relevance, data from pivotal clinical trials must be robust. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use defines robustness as a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. OPH2003 is an international, randomized, double masked, sham controlled, multi-center clinical trial. The primary endpoint, the statistical analysis of which was prespecified, is an objective anatomic endpoint based on measurements performed by a masked independent reading center. The images are analyzed by two experienced image readers, with any discrepancy of greater than 10% arbitrated by the reading center director, who is a recognized expert in the field of GA. The patients, investigators, independent reading center and we as the sponsor each remain masked throughout the duration of the entire trial, which in the case of the OPH2003 trial, means each of us remains masked until after the 18-month time-point.

In clinical trials, it is common for data for some number of subjects to be missing for assessments performed throughout the trial. The degree of data that is missing from a clinical data set can impact the robustness of the data. See above under "Statistical Analysis for Efficacy Measures" for information regarding the GA measurement data that was missing from the analysis of the primary efficacy endpoint in the OPH2003 trial, as well as a description of the sensitivity analyses we have performed. Based on our sensitivity analyses, and accounting for the data missing from our data set because of patient withdrawals or for other reasons, we believe the statistical analysis for the 12 month data from the OPH2003 trial is robust.

Although we seek to apply our enrollment criteria consistently, there may be instances where an investigator proposes a patient to participate in the trial and the reading center determines that, although a patient may not meet all criteria precisely, participation in the trial is warranted based on the overall GA pattern and size. For example, this can result in the enrollment of patients with baseline GA area slightly below 1 disc area, as was the case with one patient in each of the Zimura 4 mg group and the Part 2 sham control group (which is part of the comparison for both the Zimura 2 mg and Zimura 4 mg groups). These patients have been included in the ITT analysis for our primary efficacy endpoint. The FDA, EMA or other regulatory authorities may not agree with the inclusion of these patients in our statistical analysis, which could impact the robustness of our conclusions.

Currently, the trial is ongoing and patients continue to be treated and followed for an additional six months after the 12-month time point. We do not expect to receive the full data set with individual patient data unmasked as to treatment group until after the month 18 visit is completed for all patients. It is possible that unexpected or inconsistent findings could emerge based on additional data we receive for the period between months 12 and 18 or based on the full data set with unmasked, individual patient data. We may uncover individual patient data that causes us to re-evaluate and potentially change our initial conclusions based on the data we have received and our sensitivity analyses performed to date. Ultimately, for the OPH2003 trial to be accepted as a pivotal trial, the FDA, EMA and other regulatory authorities would need to agree that the overall data package from the OPH2003 trial and a subsequent pivotal clinical trial meet the applicable requirements and are sufficiently robust to demonstrate an acceptable safety profile, together with a clinically relevant efficacy outcome with statistical significance, and support an overall favorable benefit-to-risk determination.

Based on the foregoing, assuming that Zimura's safety profile remains consistent with findings observed to date and subject to regulatory review of the robustness of the OPH2003 trial results, we believe that one additional international, randomized, double masked, sham controlled, Phase 3 clinical trial is needed to demonstrate the safety and efficacy of Zimura in GA secondary to dry AMD in a manner sufficient to support an application for regulatory approval from the FDA and EMA in this indication. Our belief and understanding of the remaining clinical requirements to demonstrate the safety and efficacy of Zimura for the treatment of GA secondary to dry AMD in a manner sufficient to support an application for regulatory approval from the FDA and EMA is based on our review of initial, top-line data from the OPH2003 trial as well as informal discussions with the FDA. Our expectations regarding the minimum clinical requirements to demonstrate the safety and efficacy of Zimura for GA may change as 18-month clinical data from OPH2003 becomes available, and as new regulatory or third party information becomes available.

ISEE2008: Planned Phase 3 Clinical Trial Assessing Safety and Efficacy of Zimura 2 mg for GA Secondary to Dry AMD

We are in the startup phase for ISEE2008, an international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial evaluating the safety and efficacy of Zimura 2 mg in patients with GA secondary to dry AMD. We plan to enroll approximately 400 patients, who will be randomized into two groups: a first group receiving monthly administrations of Zimura 2 mg for 12 months, and a second group receiving monthly administrations of sham. The prespecified primary endpoint will be the mean rate of change in GA growth over 12 months, as measured by FAF based on readings at three time points: baseline, month 6 and month 12. At 12 months, we plan to re-randomize patients in the Zimura 2 mg arm to receive either

monthly or every other month administrations of Zimura 2 mg, and all patients receiving monthly administrations of sham will continue to receive monthly administrations of sham. The protocol provides that patients will be treated and followed for 24 months.

The key ophthalmic inclusion criteria for ISEE2008 include the following:

- non-foveal GA secondary to dry AMD;
- total GA area between 2.5 mm^2 and 17.5 mm^2, inclusive;
- if GA is multifocal, at least one focal lesion should measure 1.25 mm^2 or greater;
- GA in part within 1500 microns from the foveal center; and
- Snellen equivalent BVCA in the study eye between 20/25 and 20/320, inclusive.

As discussed above, when we initiated the OPH2003 study, we did not believe that reliable measurements of GA by FAF images for patients with CNV in the study eye could be performed. Therefore, in the clinical trial protocol for the OPH2003 trial, we indicated that patients in any arm of the trial who developed CNV in the study eye, as observed by the investigator, would be removed from the trial and any future study treatments and assessments. Based on third-party clinical data published since the OPH2003 trial commenced and discussions with our independent reading center, we believe that GA for patients developing CNV in the study eye who receive standard of care anti-VEGF treatment for the CNV, could potentially be assessed by FAF. Based on the foregoing, the protocol for ISEE2008 will provide that patients who develop CNV in the study eye will remain in the trial and continue to receive either Zimura 2 mg or sham, together with standard of care anti-VEGF treatment at the investigator's discretion. Measurements of these patients' GA will be included in the primary efficacy analysis if their FAF images can be reliably assessed by the masked reading center.

We believe that we have adequate drug supply available to begin this trial. We are in the process of engaging clinical trial sites and completing other trial initiation activities for ISEE2008, and intend to begin patient enrollment in this trial during the first quarter of 2020.

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.

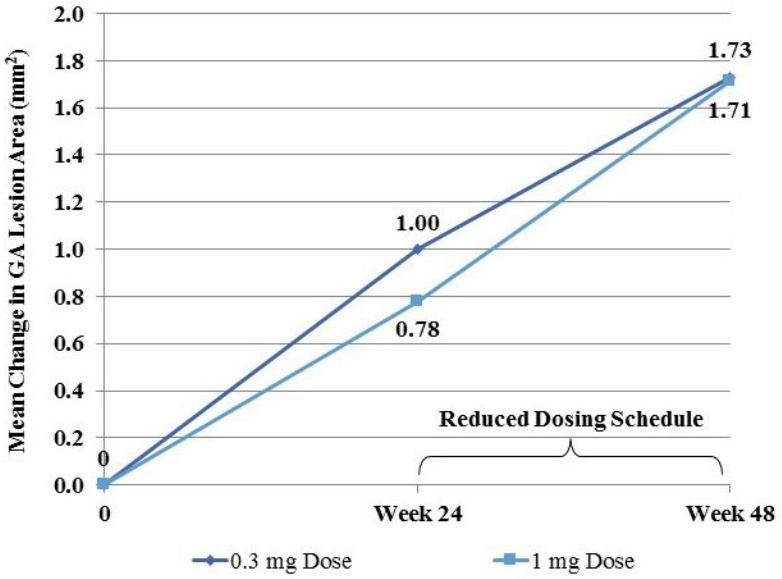
Zimura was generally well-tolerated in this trial. We did not observe any evidence of drug related adverse events. We also did not observe any incidence of conversion to wet AMD in eyes treated with Zimura. Adverse events were primarily ocular adverse events in the study eye which were related to the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

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.

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 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:

- Zimura 2 mg, followed by Zimura 2mg 14 days later, monthly for three months during an induction phase; followed by Zimura 4 mg, administered as two injections of Zimura 2 mg 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 during the second half 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.

Similar to OPH2003, OPH2005 was designed to be a Phase 2b screening trial, with the potential to demonstrate statistically significant results depending on the magnitude of the potential benefit observed. Depending on the results that are observed, OPH2005 may be a pivotal clinical trial for regulatory purposes.

This trial remains on track and we expect that 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 Lucentis 0.5 mg 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 Zimura 2 mg. 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 Lucentis 0.5 mg 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 Lucentis 0.5 mg followed by, in Group 1, Zimura 4 mg two days later and in Group 2, Zimura 2 mg 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 Lucentis 0.5 mg followed by Zimura 2 mg on the same day, followed by Zimura 2 mg fourteen days later; and

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

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 BCVA 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.

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.

HtrA1 Inhibitor Program

In October 2018, we acquired Inception 4, Inc., or 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 for other age-related retinal diseases, such as wet AMD or 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.

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

Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing, we expect to file an IND for a product candidate from this program during 2021.

Gene Therapy Research and Development Programs

Since 2017, as we evaluated our strategic priorities and the market for orphan and age-related retinal diseases with unmet medical needs, 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 option for retinal diseases. Since 2018, we have in-licensed two gene therapy product candidates and established collaborative gene therapy sponsored research programs with three leading academic research institutions in the United States. These sponsored research programs are focused on generating data to support the preclinical development of our gene therapy product candidates and discovering and developing other novel gene therapy technologies to treat a number of orphan IRDs.

The Potential of Gene Therapies for Retinal 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 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 given 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, AAV has become the most common choice for gene therapy applications inside the eye. AAV is a small, non-pathogenic 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 are focused on AAV gene therapies, 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 options 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, 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 another AAV serotype. For example, a recombinant AAV 2/5 vector is produced using the AAV2 Rep sequence and the AAV5 Cap sequence to package the transgene inside an AAV5 capsid. Because different capsid proteins have different transduction capabilities within different types of cells, 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 associated with a number of monogenic IRDs, such as the *CEP290* gene associated with LCA10 and the *ABCA4* gene associated with 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.

IC-100: 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 IC-100, our novel AAV gene therapy product candidate for the treatment of RHO-adRP. There are over 150 known mutations in the *RHO* 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" expression of the subject's innate rhodopsin, regardless of the specific mutation a subject has, with

- 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 *RHO* 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 UF 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 IC-100 and a natural history study of RHO-adRP patients.

We have also engaged a CDMO for preclinical and Phase 1/2 clinical supply of IC-100. We are conducting Phase 1/2 clinical manufacturing and other IND-enabling activities, including toxicology studies. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing and regulatory review, we plan to initiate a Phase 1/2 clinical trial for IC-100 during the fourth quarter of 2020.

IC-200: Product Candidate for BEST1-Related IRDs

In April 2019, we entered into an exclusive global license agreement with Penn and UFRF for rights to develop and commercialize IC-200, our novel AAV gene therapy product candidate for the treatment of Best disease and other *BEST1*-related IRDs. We started developing this product candidate in late 2018 after we entered into an exclusive option agreement with Penn and UFRF for these rights, which we exercised in April 2019 through the license agreement. Investigators at Penn and UFRF tested IC-200 in a naturally occurring autosomal recessive canine model for Best disease, resulting in the reversal of subretinal lesions and micro-detachments associated with the canine disease. 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 disease model with distinct phenotypic similarities to human Best disease demonstrate the potential therapeutic benefit of IC-200 for *BEST1*-related IRDs.

In October 2018, we also entered into a master sponsored research agreement with Penn (which is separate from the master sponsored research agreement for IC-100), facilitated by PCI, pursuant to which we, together with Penn, are conducting additional preclinical studies of IC-200 as well as natural history studies of patients with autosomal dominant and autosomal recessive forms of *BEST1*-related IRDs.

We have engaged a CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of IC-200. We are planning for Phase 1/2 clinical manufacturing and other IND-enabling activities. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing and regulatory review, we expect to initiate a Phase 1/2 clinical trial for IC-200 during the first half of 2021.

Minigene Programs

We are funding several sponsored research programs at UMMS seeking to use a minigene approach to develop new gene therapies for orphan IRDs. We refer to each of these programs by reference to the transgene for which we are seeking to create a minigene therapy. We receive research results from these programs as they become available. UMMS has granted us an option to obtain an exclusive license to any patents or patent applications that result from these programs. We exercised our option rights for the miniCEP290 program and in July 2019 entered into a license agreement with UMass for exclusive development and commercialization rights to patent rights and know-how for this program.

miniCEP290 Program for LCA10

Our miniCEP290 program is targeting LCA10, which is associated with mutations in the *CEP290* gene. The naturally occurring *CEP290* gene is approximately 8,000 base pairs. In a 2018 publication in *Human Gene Therapy*, researchers at UMMS presented their findings that injection of a *CEP290* minigene into a newborn mouse model for LCA10 resulted in rescue of photoreceptor cells, as evidenced by both anatomical and functional measures. The goal of the sponsored research, which we initiated in February 2018, was to create and evaluate other *CEP290* minigene constructs in the mouse model and optimize the effect observed in that publication.

We have been encouraged by the preliminary results of the sponsored research we have received to date. One of the new minigene constructs has shown five times longer duration of functional rescue of the photorecptors as compared to what

was observed in the 2018 publication. UMMS is continuing to optimize constructs with the goal of identifying a lead construct by the middle of 2020.

miniABCA4 Program for STGD1

Our miniABCA4 program is targeting STGD1, which is associated with mutations in the *ABCA4* gene. The size of the naturally occurring *ABCA4* gene is approximately 7,000 base pairs. UMMS has generated and is evaluating several *ABCA4* minigene constructs in both in vitro and in vivo experiments. We have received preliminary results and expect to receive additional results from the miniABCA4 program during the second half of 2020.

miniUSH2A Program for USH2A-Related IRDs

In July 2019, we entered into a sponsored research agreement with UMMS for our miniUSH2A program. The miniUSH2A program seeks to develop a mutation independent, minigene therapy for the vision loss associated with *USH2A* mutations, including vision loss associated with Usher 2A and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa. We expect to receive preliminary results from this program during the second half of 2020.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of Zimura, our HtrA1 inhibitors, IC-100, IC-200 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, purification 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 process that can be validated 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 aseptically filled 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.

In early 2017, we completed the small scale manufacture of multiple batches of Zimura API that we plan to use to support clinical drug supply for the ISEE2008 trial. We are in the process of recommencing manufacturing activities with our contract manufacturer, with the goal of scaling up and validating the manufacturing process to support the potential commercialization of Zimura. We will need to demonstrate that Zimura API produced through the scaled-up process is analytically comparable to the Zimura we are currently using before API manufactured through the scaled-up process can be used for commercial drug supply. We also plan to make a change to the vial used for the finished Zimura drug product during the course of the ISEE2008 trial in order to support a more efficient fill/finish operation at a commercial scale. We may need to perform additional work beyond what we currently plan to establish manufacturing and analytical capabilities sufficient to support potential commercial operations.

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, or Ajinomoto, to provide fill/finish services for Zimura. We currently obtain Zimura API from Agilent on a purchase order basis. We plan to enter into a long-term supply agreement with Agilent for the API for Zimura. 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. We also plan to enter into a long-

term supply agreement with this manufacturer for the PEG reagent. This manufacturer may need to scale up its purification process in order to support supply of PEG at a commercial scale.

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.

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, 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 by the other party.

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 and banks are comprehensively tested, including for lack of microbial contamination, 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 are designed to remove process and product-related impurities present in the harvested material, including 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. After formulation, the resulting purified AAV vector material is considered the drug substance for AAV gene therapies. The AAV drug substance is then fill/finished into vials, which results in the finished drug product and from which the injection solution is drawn.

We have engaged a gene therapy CDMO for preclinical and Phase 1/2 clinical supply of IC-100 and IC-200. We obtain the plasmids that are used for IC-100 and IC-200 from a single third-party supplier on a purchase order basis.

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. 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 approaches, and others are based on entirely different approaches. We also will face similar competition with respect to any 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 and clinical development by third parties to treat dry AMD or 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 complement system and inflammation suppression, visual cycle modulators, antioxidants and neuroprotectants, cell and gene therapies and vascular perfusion enhancers. We are aware that Apellis Pharmaceuticals, Inc., or Apellis, Roche AG, Novartis AG and MorphoSys AG, Hemera Biosciences, Inc., Gemini Therapeutics, Inc., NGM Biopharmaceuticals Inc., Gyroscope Therapeutics, Achillion Pharmaceuticals, Inc., and Biogen Inc. each have complement inhibitors in development for dry AMD, including, in the cases of Hemera Biosciences and Gyroscope Therapeutics, complement inhibitor gene therapies. We believe that the most advanced of these programs is Apellis's pegylated, synthetic peptide targeting complement protein C3. As recently as January 2020, Apellis confirmed its expectation that it would finish patient enrollment in its Phase 3 program during the early part of 2020 with the goal of enrolling approximately 1,200 patients, which would enable a primary 12-month efficacy analysis as early as the middle of 2021. If Apellis's Phase 3 program for its C3 complement inhibitor product candidate is successful, it is likely that Apellis would 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, including Allergan Inc., Allegro Ophthalmics, LLC, Alkeus Pharmaceuticals Inc., EyePoint Pharmaceuticals, Inc., Lineage Cell Therapeutics, Inc. and Stealth BioTherapeutics Corp, working in collaboration with Alexion Pharmaceuticals, Inc., are pursuing development programs for the treatment of dry AMD or GA using 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., Lin BioScience, Inc., Nightstar Therapeutics plc (prior to its acquisition by Biogen Inc.), ProQR Therapeutics N.V., Spark Therapeutics and Generation Bio Co. each have research or development programs in Stargardt disease. Three of these programs, Acucela, Alkeus 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:

- We are aware that ProQR Therapeutics N.V. is developing an RNA-based therapeutic for RHO-adRP, for which it has filed an IND and plans to enroll patients this year. We are also aware that multiple academic institutions have early stage gene therapy development programs in RHO-adRP. In addition, prior to its acquisition by Biogen Inc., Nightstar Therapeutics plc had a preclinical AAV gene therapy program in RHO-adRP. Sanofi is also exploring a potential program in this disease.

Competitive considerations for BEST1-related IRDs:

- We are aware that, prior to its acquisition by Biogen, Nightstar Therapeutics plc had a preclinical AAV gene therapy program for one or more *BEST1*-related IRDs.

Competitive considerations for LCA10:

- We are aware that Editas Medicine, Inc. (in partnership with Allergan plc) has a 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 late-stage clinical development, Generation Bio Co. has a preclinical program that utilizes ceDNA technology to target LCA10 and Oxford Biomedica plc is developing a lentiviral gene therapy program for LCA10 that is in preclinical development. In addition, several academic institutions have preclinical programs in LCA10.

Competitive considerations for USH2A-related IRDs:

- There are a number of products in preclinical research and clinical development by third parties to treat *USH2A*-related IRDs. We are aware that ProQR Therapeutics N.V. is pursuing two RNA based approaches for different mutations causing Usher 2A, one of which is currently in Phase 1/2 clinical development and the other of which is in preclinical development. We are also aware that Editas Medicine, Inc. and Odylia Therapeutics are exploring potential programs in *USH2A*-related IRDs.

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:
    - patents covering Zimura's composition-of-matter, which have issued in the United States, the countries covered by the European Patent Organisation, which we refer to as the EPO Countries, Japan and certain other jurisdictions, and which are expected to expire in Japan in 2026 and elsewhere in 2025; and patent applications covering Zimura's composition-of-matter, 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 EPO Countries, Japan and certain other jurisdictions, and which are expected to expire in the United States and Japan in 2026 and elsewhere in 2025; and

- patent applications owned by IVERIC bio, Inc.:
    - patent applications covering formulations, methods of use for treating GA, Stargardt disease and other conditions, and other proprietary technology relating to Zimura, which are pending in the United States, the EPO Countries, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2034; and
- patent applications owned by our Orion subsidiary:
    - three families of composition-of-matter and method-of-treatment patent applications covering the lead and backup compounds in our HtrA1 inhibitor program, which are pending in the United States, the EPO Countries, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2037; 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 EPO Countries, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2037 or 2039.
- patent applications in-licensed from UMass:
    - two families of composition-of-matter and method-of-treatment patent applications relating to certain proprietary minigene technology for the treatment of diseases associated with mutations in the *CEP290* gene, which are pending in the United States, the EPO Countries, Japan and certain other jurisdictions, and which, if granted, are expected to expire in 2038 or 2040.

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 a 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 EPO Countries 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 product candidates or other technologies and further 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, 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 paid Archemix an aggregate of $2.0 million in fees based on our achievement of specified clinical milestone events under the C5 License Agreement. This amount does not include the milestone payment obligation of $1.0 million triggered by the positive, initial top-line data from the OPH2003 trial.

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 $56.5 million if we achieve specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $23.5 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 for both Inception 4 and our company as the purchaser. The representations and warranties generally survived 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.

License Agreement with UFRF and Penn for IC-100

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 IC-100, our 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.

License Agreement with Penn and UFRF for IC-200

In April 2019, we entered into an exclusive global license agreement, which we refer to as the BEST1 License Agreement, with Penn and UFRF. We entered into the BEST1 License Agreement by exercising our exclusive option rights under an option agreement, or the Best1 Option Agreement, that we previously entered into with Penn and UFRF in October 2018. Under the BEST1 License Agreement, Penn and UFRF granted us a worldwide, exclusive license under specified patent rights and specified know-how and a worldwide, non-exclusive license under other specified know-how to research, develop, manufacture and commercialize certain AAV gene therapy products, including IC-200, for the treatment of Best disease and other *BEST1*-related IRDs.

We have 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 such product in at least the United States and two major European countries. In addition, we have agreed to meet specified development and regulatory milestones with respect to a licensed product by specified dates, as the same may be extended under the terms of the agreement.

We may grant sublicenses of the licensed patent rights and know-how, without the consent of Penn or UFRF, 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 to the licensed patent rights and know-how with the consent of Penn and UFRF, not to be unreasonably withheld.

Financial Terms

In May 2019, we paid Penn, for the benefit of Penn and UFRF, a $0.2 million upfront license issuance fee, which was recorded as a research and development expense, and we paid UFRF accrued patent prosecution expenses of approximately $18 thousand, which was recorded as a general and administrative expense. We have also agreed to pay Penn, for the benefit of Penn and UFRF, an annual license maintenance fee in the low double-digit thousands of dollars, which fee will be payable on an annual basis until the first commercial sale of a licensed product. In addition, we have agreed to pay Penn, for the benefit of Penn and UFRF, a one-time patent grant fee in the low triple-digit thousands of dollars, upon the issuance of a U.S. patent that claims inventions disclosed in the licensed patent rights or know-how or inventions generated under certain related sponsored research agreements with Penn or UFRF, and that is exclusively licensed to us. Furthermore, we have agreed to reimburse Penn and UFRF for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

We have further agreed to pay Penn, for the benefit of Penn and UFRF, up to an aggregate of $15.7 million if we achieve specified clinical, marketing approval and reimbursement approval milestones with respect to one licensed product, and up to an aggregate of an additional $3.1 million if we achieve these same milestones with respect to a different licensed product. In addition, we have agreed to pay Penn, for the benefit of Penn and UFRF, up to an aggregate of $48.0 million if we achieve specified commercial sales milestones with respect to one licensed product, and up to an aggregate of an additional $9.6 million if we achieve these same milestones with respect to a different licensed product.

We are also obligated to pay Penn, for the benefit of Penn and UFRF, royalties at a low single-digit percentage of net sales of licensed products. Such royalties are subject to customary deductions, credits, and 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 to patent rights or other intellectual property rights that are necessary to research, develop, manufacture and commercialize the licensed product in such country. Our obligation to pay royalties under the BEST1 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 the sale of the applicable licensed product in the country of sale;
- the expiration of regulatory exclusivity covering the applicable licensed product in the country of sale; and
- 10 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 calendar year 2032, we are also obligated to pay certain minimum royalties, not to exceed an amount in the mid tens 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 in the year the minimum royalty is paid.

If we or any of our affiliates sublicense any of the licensed patent rights to a third party, we will be obligated to pay Penn, for the benefit of Penn and UFRF, a high single-digit to a mid ten's 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 outside the scope of the BEST1 License Agreement, we will be obligated to pay Penn, for the benefit of Penn and UFRF, aggregate payments in the low double-digit millions of dollars based on certain 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 Penn, for the benefit of Penn and UFRF, a high single-digit percentage of any consideration received from such third party in connection with such sale.

Term and Termination

The BEST1 License Agreement, unless earlier terminated by us or Penn or UFRF, will expire upon the expiration of our obligation to pay royalties to Penn, for the benefit of Penn and UFRF, on net sales of licensed products. Before the effectiveness of an IND for a licensed product, we may terminate the BEST1 License Agreement with respect to such licensed product or in its entirety, at any time for any reason upon prior written notice to Penn and UFRF. Following the effectiveness of an IND for a licensed product, we may terminate the BEST1 License Agreement with respect to such licensed product by providing Penn prior written notice and a certification that we are ceasing all use, research and development and commercialization of such licensed product, subject to certain limited exceptions. We may also terminate the BEST1 License Agreement if Penn or UFRF materially breaches the BEST1 License Agreement and does not cure such breach within a specified cure period.

Penn or UFRF may terminate the BEST1 License Agreement if we materially breach the BEST1 License 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, any of our affiliates or any of our sublicensees challenge or assist a third party in challenging the validity, scope, patentability, and/or enforceability of the licensed patent rights. If we materially breach certain diligence obligations under the BEST1 License Agreement with respect to only one licensed product, then Penn and UFRF may only terminate our rights and licenses under the BEST1 License Agreement for such licensed product, but not for other licensed products.

Following any termination of the BEST1 License Agreement prior to expiration of the term of the BEST1 License Agreement, all rights to the licensed patent rights and know-how that Penn and UFRF granted to us will revert to Penn and UFRF.

License Agreement with UMass for the miniCEP290 Program

In July 2019, we entered into an Exclusive License Agreement, which we refer to as the miniCEP290 License Agreement, with UMass. We entered into the miniCEP290 License Agreement by exercising our exclusive option rights under an option agreement and a sponsored research agreement that we previously entered into with UMass in February 2018. Under the miniCEP290 License Agreement, UMass granted us a worldwide, exclusive license under specified patent rights and specified biological materials and a non-exclusive license under specified know-how to make, have made, use, offer to sell, sell, have sold and import products for the treatment of diseases associated with mutations in the *CEP290* gene, including LCA10. We may grant sublicenses of the licensed patent rights and know-how without the consent of UMass.

We have agreed to use diligent efforts to develop licensed products and to introduce such licensed products into the commercial market. Subject to obtaining marketing approval, we agreed to make any approved licensed product reasonably available to the public. In addition, we have agreed to meet specified development and regulatory milestones with respect to a licensed product by specified dates, as the same may be extended under the terms of the miniCEP290 License Agreement.

Financial Terms

In July 2019, we issued to UMass 75,000 shares of our common stock following execution of the miniCEP290 License Agreement pursuant to an exemption from registration afforded by Section 4(a)(2) of the Securities Act of 1933, as amended, or the Securities Act. In September 2019, we paid UMass a $0.4 million upfront license fee, which was recorded as a

research and development expense, and we paid UMass accrued patent prosecution expenses of approximately $18 thousand, which was recorded as a general and administrative expense.

We have also agreed to pay UMass an annual license maintenance fee in the low double-digit thousands of dollars, which fee will be payable on an annual basis until the expiration of the royalty term for the licensed products. Furthermore, we have agreed to reimburse UMass for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

We have further agreed to pay UMass up to an aggregate of $14.75 million in cash and issue up to 75,000 shares of our common stock if we achieve specified clinical and regulatory milestones with respect to a licensed product. In addition, we have agreed to pay UMass up to an aggregate of $48.0 million if we achieve specified commercial sales milestones with respect to a licensed product.

We are also obligated to pay UMass royalties at a low single-digit percentage of net sales of licensed products. Our obligation to pay royalties under the miniCEP290 License Agreement will continue on a licensed product-by-licensed product and country-by-country basis until the later of: (a) the expiration of the last-to-expire licensed patent rights covering the sale of the applicable licensed product in the country of sale, or (b) 10 years from the first commercial sale of the applicable licensed product in the country of sale. Beginning with the calendar year following receipt of marketing approval for a licensed product, we are also obligated to pay certain minimum royalties, not to exceed an amount in the mid-double-digit 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 in the year the minimum royalty is paid.

If we or any of our affiliates sublicenses any of the licensed patent rights or know-how to a third party, we will be obligated to pay UMass a high single-digit to a mid-tens percentage of the consideration received in exchange for such sublicense, with the applicable percentage based upon the stage of development of the licensed products at the time we or the applicable affiliate enters into the sublicense.

If we receive a rare pediatric disease priority review voucher, or a 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 outside the scope of the miniCEP290 License Agreement, we will be obligated to pay UMass a low-tens percentage of the fair market value of the priority review voucher at the time of approval of such product candidate and a low-twenties percentage of the fair market value of the priority review voucher at the time of achievement of a specified commercial sales milestone for such other product candidate. In addition, if we sell such a priority review voucher to a third party, we will be obligated to pay UMass a low-thirties percentage of any consideration received from such third party in connection with such sale.

Term and Termination

The miniCEP290 License Agreement, unless earlier terminated by us or UMass, will expire upon the expiration of our obligation to pay royalties to UMass on net sales of licensed products. We may terminate the miniCEP290 License Agreement at any time for any reason upon prior written notice to UMass. We may also terminate the miniCEP290 License Agreement if UMass materially breaches the miniCEP290 License Agreement and does not cure such breach within a specified cure period.

UMass may terminate the miniCEP290 License Agreement if we materially breach the miniCEP290 License Agreement and do not cure such breach within a specified cure period.

Following any termination of the miniCEP290 License Agreement prior to expiration of the term of the miniCEP290 License Agreement, all rights to the licensed patent rights and know-how that UMass granted to us will revert to UMass.

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;
- completion of the manufacture, under current Good Manufacturing Practices, or cGMP, conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical and stability testing;
- 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 trial 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 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 drug or biologic with potential therapeutic value in humans, the product candidate must undergo preclinical testing. 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 or re-commence.

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 certain available data from the study to which only the DSMB may access. 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 to 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 GCPs and the integrity of the clinical data submitted.

For a detailed discussion of how these regulatory requirements apply to Zimura and its potential approval for the treatment of GA secondary to dry AMD, please see the above section entitled, "*Zimura - Zimura Dry AMD Trials - OPH2003 Ongoing Clinical Trial Assessing the Safety and Efficacy of Various Doses of Zimura for GA Secondary to Dry AMD - Requirements for Regulatory Approval of Zimura in GA*".

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. Expanded access allows a patient to obtain an investigational new drug when enrolling in a clinical trial for that drug is difficult or not feasible for the patient. 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, subject to FDA approval. There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act, or Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available.

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 needing FDA approval under the expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients under the Right to Try Act.

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. The NIH, including its Novel and Exceptional Technology and Research Advisory Committee, or NExTRAC, also advises the FDA on gene therapy issues and other issues related to emerging biotechnologies. The FDA and the NIH have published guidance documents relating to the development and submission of gene therapy protocols.

The FDA has issued various guidance documents regarding gene therapies, including recent final guidance documents released in January 2020 relating to chemistry, manufacturing and controls information for gene therapy INDs, long-term follow-up after the administration of gene therapy products, gene therapies for rare diseases and gene therapies for retinal disorders. Although the FDA has indicated that these and other guidance documents it previously issued 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 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.

Until 2019, most gene therapy clinical trials required pre-review by the predecessor of NExTRAC before being submitted for approval by the IRBs and any local biosafety boards. In 2019, the NIH eliminated the pre-review process and going forward, the review of future gene therapy clinical trial protocols would be largely handled by IRBs. Furthermore, in 2019, the NIH removed from public access the Genetic Modification Clinical Research Information System (GeMCRIS) database, which previously contained substantial amounts of safety and other patient information regarding human gene therapy studies performed to date.

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 for marketing approval. 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 2020 is $2,942,965 for an application requiring clinical data. The sponsor of an approved application is also subject to an annual program fee, which for fiscal year 2020 is $325,424. 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 any 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 Drug Administration Safety and Innovation Act, or FDASIA, 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 before beginning 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, including AMD.

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 inspections 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'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.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations and Accelerated Approval; Rare Pediatric Disease Priority Review Voucher Program

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life–threatening disease or condition. These programs are fast track designation, breakthrough therapy designation, priority review designation and regenerative advanced therapy designation. The FDA may also approve certain products based on an accelerated basis.

Specifically, 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. 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.

FDASIA 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.

The FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case by case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement

may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment–limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

With passage of the Cures Act, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, and potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

The FDA may grant accelerated approval to a product for a serious or life–threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

Finally, the FDA may award priority review vouchers to sponsors of rare pediatric disease product applications that meet certain criteria. A rare pediatric disease is a rare disease where the disease is serious or life-threatening with the serious or life-threatening manifestations primarily affecting individuals from age zero to 18. A sponsor who receives approval for a drug or biologic for a rare pediatric disease may qualify for a priority review voucher, which the sponsor may redeem to receive priority review of a subsequent marketing application for a different product. In lieu of using the voucher for one of its own product candidates, a sponsor may sell that voucher for use by a third party. Current prices for these vouchers range in the hundreds of millions of dollars. The current rare pediatric disease priority review voucher program will expire in October 2020, unless Congress renews the program, although a drug designated as a rare pediatric disease treatment can still receive a priority review voucher if the marketing approval application for the drug is submitted and the drug is approved by October 2022.

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 label changes, 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. Although health care providers may prescribe products for off-label uses in their professional judgment, drug manufacturers are prohibited from soliciting, encouraging or promoting unapproved uses of a product.

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 is 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 responsible for the pharmacological 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 Patient Protection and Affordable Care Act, or ACA, 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. A biosimilar is a biological product that is highly similar to an existing FDA-licensed "reference product." As of January 1, 2020, the FDA had approved 26 biosimilar products for use in the United States. No interchangeable biosimilars, as described below, have been approved as of January 1, 2020. The FDA has issued several guidance documents outlining an approach to the review and approval of biosimilars.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is biosimilar to a 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. Since the passage of the BPCIA, many states have passed laws or amendments to laws, including laws governing pharmacy practices, which are state-regulated, to regulate the use of biosimilars.

Patent Term Extension

A patent claiming a new drug product, its method of use or its method of manufacture 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 the 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 the "same product" for purposes of orphan drug exclusivity remains in flux in the context of gene therapies, and the FDA has issued recent draft guidance suggesting that it would not consider two gene therapy products to be different products solely based on minor differences in the transgenes or vectors. 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.

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 that the product is 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 before beginning clinical trials or marketing 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

Under the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, an applicant must obtain prior 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 regulation 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, 2020, 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 regulation would come into effect six months after the European Commission publishes a notice of this confirmation. The website indicated that the audit was expected to commence in December 2020.

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 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. Manufacturers 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.

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 for human use. Regulation 1394/2007/EC includes specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products. All advanced therapy medicinal products are approved centrally through the EMA. The EMA's Committee for Advanced Therapies reviews and provides an opinion regarding each advanced therapy MAA for potential final approval by the European Commission.

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 detailing the continued quality, safety and efficacy of the product, 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 European Union market, in the case of the centralized procedure, or in 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.

Patent Term Extensions in the European Union and Other Jurisdictions

The European Union also provides for patent term extension through Supplementary Protection Certificates, or SPCs. The rules and requirements for obtaining a SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. These periods can be extended for six additional months if pediatric exclusivity is obtained, which is described in detail below. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union.

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. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator’s data in 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 European Union 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 that are shown, during the scientific evaluation prior to authorization, 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 marketing 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 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 new 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 to not justify maintenance of market exclusivity.

Pediatric Studies and Exclusivity

Before 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 SPC.

Brexit and the Regulatory Framework in the United Kingdom

In June 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as “Brexit”. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020. There is a transitional period currently scheduled to remain in effect until December 31, 2020, during which the United Kingdom government and the European Union are attempting to agree to long-term trade and other agreements. Since the existing regulatory framework for pharmaceutical products in the United Kingdom is derived from European Union directives and regulations, which the United Kingdom could abandon or modify in the future, Brexit could materially impact the future regulatory regime for pharmaceutical products in the United Kingdom.

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 medically necessary or cost effective by the payors. 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 products for AMD, for which 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, and since then, similar proposals from HHS and CMS have followed. For example, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, would allow states and certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants would be required to demonstrate that their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, the FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries.

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 access to certain products, 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 which 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, if and 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. EU 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 EU Member States 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 EU 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 from 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 subject to a penalty. The individual mandate was repealed as part of the Tax Cuts and Jobs Act of 2017, or TCJA, 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, and this proceeding is currently on appeal at the U.S. Supreme Court. If upheld by the Supreme Court, the effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace and providers will be uncertain.

In addition, in December 2018, the U.S. District Court of the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and non-severable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The Trump Administration and CMS have both stated that the ruling will have no immediate effect, and later in December 2018, the same court issued an order staying the judgment pending appeal. In December 2019, the U.S. Circuit Court of Appeals for the Fifth Circuit affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. In January 2020, the U.S. Supreme Court declined to review this decision on an expedited basis.

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, 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;

- 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, among other things, prohibits 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 Act, and their respective implementing regulations, which impose obligations, including mandatory contractual terms, relating to safeguarding the privacy, security and transmission of individually identifiable health information by certain covered entities and their business associates;

- 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 Foreign Corrupt Practices Act, which, among other things, prohibits providing or offering to provide money or anything of value to a foreign government body, government official, or political candidate for the improper purpose of obtaining or keeping business;

- federal transparency requirements such as the federal Physician Payments Sunshine Act, created under the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to 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 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, 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, 2020, we had 38 full-time employees, including a total of 9 employees with M.D. or Ph.D. degrees. Of our workforce, 20 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. We changed our corporate name from Ophthotech Corporation to IVERIC bio, Inc. in April 2019. 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.ivericbio.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 research and development programs, including our ongoing and future clinical trials for Zimura, our preclinical development programs for IC-100 and IC-200, our collaborative gene therapy sponsored research programs, and our preclinical development program for our HtrA1 inhibitors. 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 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 commercializing pharmaceutical products. 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. 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 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, funds we received under our prior Fovista licensing and commercialization agreement with Novartis Pharma AG, funds we received in connection with our acquisition of Inception 4 in October 2018, and our follow-on public offerings, which we closed in February 2014 and December 2019. As of December 31, 2019, we had an accumulated deficit of $480.5 million. Our net loss was $58.9 million for the twelve months ended December 31, 2019 and we expect to continue to incur significant operating losses for the foreseeable future.

Zimura is in clinical development, our gene therapy product candidates IC-100 and IC-200 and our HtrA1 inhibitor program are each in preclinical development, and we are funding multiple ongoing collaborative gene therapy sponsored

research programs. We expect our research and development expenses to increase as we pursue these programs as currently planned and as we initiate ISEE2008, our planned Phase 3 clinical trial for Zimura in GA. 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 Corp. with respect to Zimura, UFRF and Penn with respect to IC-100 and IC-200, UMMS with respect to any potential product candidates from our miniCEP290 program, and the former equityholders of Inception 4 with respect to our HtrA1 inhibitor program, in each case, that impose significant milestone payment obligations on us if we achieve 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 IC-100, IC-200 and any product candidates we choose to develop from our miniCEP290 program. It is likely that any future in-licensing or acquisition agreements that we enter into with respect to additional product candidates or technologies would include similar obligations.

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

- continue the development of Zimura in GA and STGD1;
- continue the development of IC-100 and IC-200 and pursue our collaborative gene therapy sponsored research programs;
- continue the preclinical development of our HtrA1 inhibitor program;
- in-license or acquire the rights to, and pursue the development of, other product candidates or technologies;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, manufacturing, quality control, quality assurance and scientific personnel;
- 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 our future growth.

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 or sooner than we currently expect.

As of December 31, 2019, we had cash and cash equivalents of $125.7 million. We believe that our cash and cash equivalents will be sufficient to fund our operations and capital expenditure requirements as currently planned into the beginning of 2022. In addition, we estimate that our year-end 2020 cash and cash equivalents will range between $60 million and $70 million. These estimates are based on our current business plan, including the continuation of our current research and development programs including the ISEE2008 trial. These estimates do not reflect any additional expenditures, including associated development costs, in the event we in-license or acquire any new product candidates or commence any new sponsored research programs. We have based these estimates on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

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. Although 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 total remaining costs necessary to complete development, to complete process development and manufacturing scale-up and validation activities and to potentially seek marketing approval for any of our product candidates.

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

- the scope, progress, costs and results of our current and planned Zimura clinical programs;
- the scope, progress, costs and results of our efforts to develop IC-100 and IC-200, including activities to establish manufacturing capabilities and preclinical testing to enable us to file INDs for these product candidates;
- the scope, progress, costs and results from our collaborative gene therapy sponsored research programs, including costs related to the in-license and future development of any promising product candidates and technologies that emerge from these programs;
- the scope, progress, costs and results of our efforts to develop our HtrA1 inhibitor program, including activities to establish manufacturing capabilities and formulation development and other preclinical development activities to enable us to file an IND for a product candidate from this program;
- the costs, progress and timing of process development, manufacturing scale-up and validation activities, analytical development 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 product candidates or technologies;
- our ability to establish collaborations on favorable terms, if at all, if we choose to do so, including any collaboration for the further development and potential commercialization of Zimura;
- 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, 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. Although we were able to raise approximately $42.6 million in net proceeds through our December 2019 public offering, we may not be able to successfully raise additional capital in the future. The size of our company and our status as a company listed on The Nasdaq Global Select 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 issue such shares at a premium, which investors may be unwilling to accept, or 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.

We may require additional funding beyond what we currently expect due to unforeseen or other reasons. Our costs may exceed our expectations if we experience any unforeseen issue in our ongoing clinical trials, such as issues with patient enrollment, the retention of enrolled patients or 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 modify or 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. For example, we plan to begin the ISEE2008 trial, which is a single Phase 3 clinical trial evaluating Zimura for GA, with the expectation that data collected from such trial, if it is positive, together with data from our OPH2003 trial, will be sufficient to seek marketing approval in the United States and the European Union and we may subsequently decide to, or be required by regulatory authorities to, enroll additional patients in the ISEE2008 trial beyond our current expectations or conduct additional clinical trials for Zimura in GA in order to seek or maintain regulatory approval or qualify for reimbursement approval. As a result of any of the above, 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 equity issuances 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 have issued, and may in the future issue additional, equity securities as consideration for 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 an aggregate of 5,174,727 shares of our common stock as up-front consideration to the former equityholders of Inception 4. 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 under the Inception 4 Merger Agreement, 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 our acquisition of Inception 4, and will be payable in cash thereafter. In July 2019, we also issued 75,000 shares of our common stock to UMMS as partial upfront consideration for the in-license of our miniCEP290 program, and are obligated to issue up to 75,000 additional shares to UMMS upon the achievement of a development milestone.

In August 2018, we entered into an 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 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.

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.

Our strategy of obtaining additional rights to products, product candidates or technologies for the treatment of retinal diseases may not be successful.

An element of our strategy has been to expand our pipeline through 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. Since early 2018, we have completed multiple acquisition, in-license, exclusive option and sponsored research arrangements for product candidates and other technologies intended to treat retinal diseases. We plan to continue to evaluate additional opportunities to in-license or acquire products, product candidates and technologies on a selective and targeted basis. We may also continue to consider other alternatives, including mergers or other transactions involving our company as a whole or other collaboration transactions, including collaboration or out-license opportunities for further development and potential commercialization of Zimura. 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. There are currently a limited number of available product candidates or technologies for the treatment of diseases affecting retina and the competition for those assets is intense. The process of proposing, negotiating and implementing a license or acquisition of a product candidate is lengthy and complex. With respect to potential product candidates or technologies for which we have entered into option agreements or sponsored research agreements for which we have option rights, our agreements generally do not have fixed economic or other key terms for definitive agreements, and we may not obtain favorable terms if and when we choose to exercise our options to acquire or in-license any product candidates or technologies.

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 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 priming 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 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 or in-license 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 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 candidate 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 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 compared 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 collaborators 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 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 and certain of our current and former board members and 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. Certain current and former members of our board of directors and 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. In September 2019, the court issued an order dismissing some, but not all, of the allegations in the class action lawsuit and denied our motion to dismiss the shareholder derivative action. The class action lawsuit is currently in the discovery phase. We and the defendants continue to 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 lawsuits may be filed.

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 we may evaluate as part of our collaborative gene therapy sponsored research programs;
- making arrangements with third-party manufacturers and providers of starting materials for our product candidates, and having those manufacturers successfully develop manufacturing processes for drug substance and

drug product and provide adequate amounts of drug product for preclinical and clinical activities in accordance with our expectations and regulatory requirements;

- 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 for scale-up and commercial manufacturing, receiving regulatory approval of our manufacturing processes and our third-party manufacturers' facilities and ensuring adequate supply of drug substance and drug product and starting materials used for the manufacture of drug substance and drug product;
- establishing sales, marketing and distribution capabilities, either internally or through collaborations or other arrangements, to effectively market and sell our product candidates, if and when approved;
- 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 Federal Food, Drug and Cosmetic Act, or 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 clinical development, 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. Drug research, including the gene therapy research we are sponsoring with UMMS, may never yield a product candidate for preclinical or clinical development. Early stage and later stage research experiments and preclinical studies, including the ongoing preclinical studies pursuant to our sponsored research programs with Penn and other preclinical studies for IC-100 and IC-200, 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, including a large Phase 2b trial with statistically significant efficacy signal. Furthermore, our Phase 2a OPH2007 safety trial of Zimura in combination with the anti-VEGF agent Lucentis in wet AMD did not replicate the results of our Phase 1/2a OPH2000 trial. Additionally, although the results we have received to date from our OPH2003 trial confirm that Zimura met the prespecified primary endpoint in reducing the mean rate of GA growth in patients with dry AMD with statistical significance across both the Zimura 2 mg and Zimura 4 mg treatment groups when compared to the corresponding sham control groups, these results may be undermined by inconsistent data obtained from the final results from this clinical trial or may not be replicated in the planned ISEE2008 trial or any other future trial we may conduct for Zimura in GA. 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 trials for any preclinical product candidates that we are developing or may wish to in-license or acquire;
- 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 for any number of reasons, including as a result 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, distribution, storage and import/export of materials and products;
- we or our contract research organizations may be unable to complete necessary analytical development for and testing of our product candidates, including assays for assessing the potency of our gene therapy product candidates;
- regulators or institutional review boards may not agree with our clinical trial designs, 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 trials 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 those 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; and
- the cost of clinical trials of our product candidates may be greater than we anticipate.

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 ongoing efforts, we may not complete any of our ongoing or planned development activities for our product candidates. The timing of the completion of, and the availability of results from, development activities, especially clinical trials, is difficult to predict. For clinical trials in particular, we do not know whether they 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. For example, our expectations regarding the remaining clinical requirements to demonstrate the safety and efficacy of Zimura for the treatment of GA secondary to dry AMD in a manner sufficient to support an application for regulatory approval to the FDA and EMA are based on our review of initial, top-line data from the OPH2003 trial as well as informal discussions with the FDA. Although we have submitted the protocol for the ISEE2008 trial to the FDA, we do not currently plan to have any additional or formal interactions with the FDA before enrolling patients in the trial. Our expectations regarding the minimum clinical requirements to demonstrate the safety and efficacy of Zimura for GA could be incorrect or may change as we continue to review and analyze data from our OPH2003 trial, including the 18-month data set when it becomes available, as we continue to plan for and as we conduct our ISEE2008 trial, and as new regulatory or third party information, including third-party clinical data or information from prospective collaborators or licensees, becomes available. If we experience delays in manufacturing, testing or marketing approvals, our product development costs would increase. Significant product development delays also could allow our competitors to bring products to market before we do, could impair our ability to successfully commercialize our product candidates, including by shortening any periods during which we may have the exclusive right to commercialize our product candidates, and may otherwise harm our business and results of operations.

Our development of Zimura is based on a novel mechanism of action that is unproven in GA and STGD1 and poses a number of scientific and other risks, and we may not be successful in developing Zimura in the indications we are pursuing.

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, and that the 12-month top-line data from our OPH2003 trial of Zimura in GA support our view, 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. There have been other investigational products using complement inhibition as a mechanism of action for the treatment of GA, including inhibition of C5, that proved to be unsuccessful, even in later stage clinical trials. Even though our OPH2003 trial of Zimura in GA met its prespecified primary endpoint, this mechanism of action may not prove safe and effective for the treatment of GA, STGD1 or any other indication for which we may develop Zimura.

The 12-month results we observed from the OPH2003 trial may not be supported by the final results of this trial or may not be fully replicated in the ISEE2008 trial. The 18-month results for OPH2003, for which we will not be evaluating the statistical significance of the efficacy data, may not be consistent with or comparable to the 12-month results. The ISEE2008 trial may yield results that are different from the 12-month results observed in the OPH2003 trial.

The 12-month results we observed from our OPH2003 trial of Zimura in GA may not be supported by the final results of this trial or may not be fully replicated in the ISEE2008 trial. In accordance with the OPH2003 trial protocol, we will continue to treat and follow patients through the 18-month time point to collect additional safety and efficacy data, including mean GA area and mean change in BCVA and LL BCVA by treatment group. Although we do not plan to perform any prespecified statistical analysis with respect to these data, these data may indicate an unexpected or unknown safety issue, including increased incidence of CNV, or may indicate the loss of efficacy for Zimura during the period between month 12 and month 18. After month 18, we expect to receive and analyze individual patient data on an unmasked basis following completion of the trial by all patients. We expect that the unmasked individual patient data will provide us a better understanding of the results and the variables affecting the results, although it may indicate that our initial conclusions were not well founded due to inconsistencies, data entry errors or because of unknown variables or patient sub-groups that could potentially be driving the results in one or more treatment groups. At this time, we cannot verify that GA images have been measured accurately or review the images for consistency with our hypotheses and the conclusions from this trial. Since the 18-month efficacy data analysis is descriptive only, it may not be relevant to draw any conclusions other than regarding the safety of Zimura. Additionally, patients may drop out from the trial between month 12 and month 18 in a greater number than we expect, which may also hamper our ability to draw conclusions from the 18-month data.

Unlike the OPH2003 trial, the ISEE2008 trial will include only one treatment arm, Zimura 2 mg, in addition to a control arm. Several Phase 3 clinical trials for ophthalmic product candidates that have been, or are currently being, conducted by other sponsors include multiple treatment arms, either different doses or treatment regimens, in addition to a control arm. The FDA has expressed that including multiple doses or treatment regimens within a single trial helps mitigate the risk of bias in the trial. We believe that the anatomical measure used as the primary efficacy endpoint in our OPH2003 trial, the mean rate of change in GA growth, as evaluated by an independent, masked reading center, is not subject to bias. We have decided to proceed with only one treatment arm in the ISEE2008 trial consisting of a single monthly administration of Zimura 2 mg, because the 12-month data from the OPH2003 trial suggested that monthly administration of Zimura 2 mg provides a similar benefit (approximately 27%) in reducing the mean rate of GA growth over 12 months as compared to the corresponding sham control group, as measured by our primary endpoint, as Zimura 4 mg and because we want to avoid the treatment burden associated with the Zimura 4 mg dose evaluated in our OPH2003 trial. Additionally, because we want to begin to evaluate the efficacy of a less frequent dosing regimen, we plan to re-randomize the patients in the monthly Zimura 2 mg treatment arm at 12 months and evaluate dosing Zimura 2 mg every other month, a dosing regimen which we have not previously studied, in half of those patients during the second 12 months of the trial. The ISEE2008 trial, however, is not designed to reliably assess any differences we observe between these treatment groups at 24 months with statistical significance and the label we would seek for Zimura in GA, if the results from the ISEE2008 trial are positive, would in all likelihood provide for monthly administration of Zimura.

We plan to conduct the ISEE2008 trial at many clinical centers that were not included in the OPH2003 trial. The introduction of new centers, and the resulting involvement of new treating physicians, can introduce additional variability into the conduct of the trials in accordance with their protocols and may result in greater variability of patient outcomes, which could adversely affect our ability to detect statistically significant differences between patients treated with Zimura 2 mg and patients receiving sham control.

In addition, the 12-month data from the OPH2003 trial suggested there is an overall dose response relationship in which higher doses of Zimura corresponded to a greater reduction in the mean rate of GA growth as compared to the corresponding sham group. For our ISEE2008 trial, for the reasons stated above, we have decided to proceed with only a 2 mg dose treatment arm and not include a 4 mg dose treatment arm. The 2 mg dose may prove to not be efficacious in treating GA. Additionally, unlike the protocol for the OPH2003 trial, the protocol of the ISEE2008 trial will provide that patients who develop CNV in the study eye in the trial may, at the investigator's discretion, remain in the trial and receive standard of care anti-VEGF therapy, and that measurements of these patients' GA will be included in the primary efficacy analysis if their FAF images can be reliably assessed by the masked reading center. If a significant number of patients develop CNV in the study eye and these patients' FAF images are not reliably assessable, or if more patients than we anticipate drop out or their data is

otherwise missing, it would reduce the number of patients from whom data is available for analyzing the primary endpoint for this trial and the ISEE2008 trial could be underpowered to demonstrate a potential clinical benefit for Zimura in GA with statistical significance.

Our intended regulatory pathway for generating sufficient safety and efficacy data to submit an NDA and potentially obtain marketing approval for Zimura for GA is subject to a number of assumptions, including that we may be able to rely on the results from our OPH2003 trial as one of two well-controlled, pivotal trials typically required by the FDA. The FDA, EMA and other regulatory authorities may not accept the results of the OPH2003 trial as a pivotal clinical trial, or may not agree with our selection of the primary endpoint for the OPH2003 and ISEE2008 trials or the statistical analysis we performed. We may decide to or may be required to enroll additional patients, collect additional safety data or conduct additional clinical trials to seek or obtain approval for Zimura in GA.

Based on the 12-month results we have received from our OPH2003 trial, additional statistical analysis we have performed and informal discussions we have had with the FDA, we believe that the efficacy results from this trial could potentially satisfy the FDA's requirements as one of the two pivotal clinical trials typically required for marketing approval. This belief is based on many assumptions, including that a reduction in mean rate of GA growth is a primary endpoint of clinical relevance, in the absence of a demonstrated reduction in the loss of vision, and that data from the OPH2003 trial is robust. The FDA, the EMA or other regulatory authorities may not agree with our view that the observed reduction in the rate of GA growth is clinically relevant or meaningful, or may require us to correlate this reduction in rate of GA growth with another outcome more directly associated with visual function. We are not currently planning to include vision as a primary or secondary efficacy endpoint in the ISEE2008 trial and it will be assessed as a safety endpoint. The FDA, the EMA or other regulatory authorities may disagree with our conclusion regarding the robustness of the data from the OPH2003 trial based on our sensitivity analyses or may conduct their own sensitivity analyses yielding different results. We likely will not have an opportunity to obtain definitive confirmation from the FDA, EMA or other regulatory authorities regarding the robustness of the data from our clinical trials, including the OPH2003 trial, until such time as we submit an application for regulatory approval and receive a response from the applicable authority. If the OPH2003 trial results are not considered robust, in order to seek marketing approval we may need to conduct, in addition to the ISEE2008 trial, one or more additional, well-controlled clinical trials that meets the applicable regulatory requirements in order to obtain sufficiently robust data to support regulatory approval.

The FDA, EMA or other regulatory authorities may not agree with the methodologies we used to perform the statistical analysis of the OPH2003 trial results. In particular, they may not agree with how we performed the comparisons of patients receiving Zimura 2 mg with patients in the sham groups, as the comparisons draw upon patients that were enrolled into two different parts of the trial, using different randomization ratios and different vision criteria. In addition, they may not agree with the validity of our MRM analysis, which imputes the values of missing data based on observed data. We plan to use the same MRM analysis in the ISEE2008 trial. Moreover, the FDA, EMA or other regulatory authorities may disagree with our inclusion in our efficacy analysis of patients who do not strictly meet all eligibility criteria, or whose treatment or assessments in the clinical trial deviated from the clinical trial protocol on one or more occasions. The FDA, EMA or other regulatory authorities may take issue with the degree of data that are missing from the clinical data set from our OPH2003 trial, or with the rate at which patients withdrew from the trial.

Although we believe that our OPH2003 trial was well-controlled, with appropriate eligibility criteria and appropriate stratification for baseline characteristics, the FDA, EMA or other regulatory authorities may not agree with the methodologies we used to determine patient eligibility and randomize patients to the various treatment groups and therefore may not agree that the comparisons we have made for mean rate of GA growth are statistically valid. The FDA, EMA or other regulatory authorities may take issue with the number of modifications we introduced to the OPH2003 trial following its commencement, which they may view as introducing additional uncontrolled variables, invalidating the comparisons across groups. In particular, the FDA, EMA or other regulatory authorities may view the change in enrollment criteria applied in the various modifications as changing the nature of the patients enrolled, thus rendering the results of the trial as uninterpretable, or may disagree with our decision to remove patients who develop CNV in their study eye from future treatments and assessments as inappropriate, concluding that it may have resulted in unmitigated or uncontrolled bias in the efficacy results from the trial.

Based on informal discussions with the FDA, we believe we need to conduct one additional clinical trial with enough patients such that we will have safety data for a minimum of 300 patients having received the dose of Zimura for which we are seeking approval, or a higher Zimura dose, independent of indication, for a minimum of 12 months, with 24-month safety data available for some portion, but not all, of these 300 patients. This additional clinical trial would need to be well-controlled, with a primary efficacy analysis at the 12 month time point or later. We believe that if we were to file an application for marketing approval for Zimura for GA, we would be able to rely on safety data from our OPH2003 and ISEE2008 trials in GA, as well as our OPH2005 trial evaluating Zimura for STGD1. We also believe that, if the data from the ISEE2008 trial are positive, we would be able to submit our application following the primary efficacy analysis for the ISEE2008 study at the 12-month time

point, without waiting for the full 24-month data package, that we could continue collecting data after submitting for marketing approval and that we could supplement our applications for marketing approval while they are pending. We have designed our ISEE2008 trial to meet these requirements, which, as we understand them, and if data from the ISEE2008 trial are positive, will permit us to seek marketing approval for Zimura in GA in the United States and potentially the European Union. We have not had formal interactions with either the FDA or the EMA regarding the ISEE2008 trial and may not do so before receiving results from the trial and submitting our applications for marketing approval. In addition, we may engage formally or informally with regulatory authorities, including competent authorities at the national level in Europe, during the trial and receive feedback that is not consistent with our expectations, including potential disagreements by the EMA and other regulatory authorities with what we are understand are the requirements of the FDA. Regulatory authorities may require us to enroll additional patients, collect additional safety data, conduct additional trials or take other actions, which would require us to revise our development plans for Zimura, including potentially changing the design of the ISEE2008 trial, increase the costs of our Zimura clinical programs and delay our expected timelines. In addition, we may experience a higher than anticipated drop out rate in our ISEE2008 trial, which could result in our not having safety data for a sufficient number of patients, even if the results from the ISEE2008 are otherwise positive.

Furthermore, our previous and ongoing Zimura clinical trials have evaluated Zimura dosing levels and regimens that we have studied only in cohorts consisting of a small number of patients. This approach may increase the risk that patients in our ongoing 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 by the investigators to the drug product in our OPH2003 trial, previously unobserved adverse events and/or serious adverse events may manifest in the remaining portion of our OPH2003 trial, in our OPH2005 trial, in our planned ISEE2008 trial or in any other subsequent clinical trials we or a potential licensee or collaborator may undertake for Zimura. When we follow patients for a longer period of time or collect safety data from a greater number of patients, we may observe safety events that we have not previously observed. 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.*"

Because the primary efficacy endpoint and the statistical analysis plan we would expect to use to analyze data for the primary efficacy endpoint for our ISEE2008 trial are similar to those of the OPH2003 trial, any disagreements by the FDA, EMA or other regulatory authorities with OPH2003 will likely affect ISEE2008 as well. Our ongoing and planned clinical trials and any other future clinical trials for Zimura that we or a potential future licensee or collaborator may undertake 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 planned or any other future clinical trials for Zimura could adversely affect our business and the value of your investment in our company.

We have no human clinical data regarding the safety and efficacy of Zimura as a treatment of STGD1. The drop-out rate may reduce the number of patients from whom we can collect and analyze data from our OPH2005 trial.

We have no human clinical data regarding the safety and efficacy of Zimura as a treatment for STGD1. 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 during the second half 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 Stargardt disease, like GA, is a degenerative disease, 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 OPH2005 trial, who may be younger and may experience vision loss that is more subtle than patients with GA or AMD, may not perceive a benefit from continuing to participate and therefore may drop out of this trial. Although we and the investigators and their staff take efforts to encourage continued patient participation, the drop-out rate 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 this trial. Given the information above, our OPH2005 trial could be underpowered to demonstrate a potential clinical benefit for Zimura in STGD1 with statistical significance.

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

Gene therapy is an emerging field of drug development with only two gene replacement therapies having received FDA approval to date. Our gene therapy research and development programs, which we decided to undertake based on a review of a limited set of preclinical data, are still at an early stage. Even with promising preclinical data, there remains several areas of drug development risk, including translational science, manufacturing materials and processes, safety concerns, regulatory pathway and clinical trial design and execution, which pose particular uncertainty for our programs given the relatively limited development history of, and our limited prior experience with, gene therapies. Furthermore, the medical community's understanding of the genetic causes of many diseases continues to evolve and further research may change the medical community's views on what therapies and approaches are most effective for addressing certain diseases.

For example, while there are more than 200 known mutations to the *BEST1* gene, the different types of mutations and their association with various *BEST1*-related IRDs are still not well-understood. Our product candidate for these diseases, IC-200, may only be effective in treating retinal diseases associated with certain mutations in the *BEST1* gene and not other mutations. Additionally, we decided to in-license and pursue the development of IC-200 based on results observed in an autosomal recessive canine disease model. A majority of humans with *BEST1*-related IRDs, however, have the autosomal dominant form of the disease, commonly referred to as Best disease. If we choose to develop IC-200 for this patient population, using a construct previously studied in an autosomal recessive canine disease model, this approach may ultimately prove ineffective.

For our miniCEP290 program and other minigene programs, we are sponsoring research using a novel approach that is largely untested and presents various scientific and regulatory risks. To date, all the data generated for our miniCEP290 program are in a newborn mouse model for LCA10, and we do not know whether the effect we observed with these minigenes in mice will be replicated in other animals or humans. Furthermore, minigenes result in the expression of a protein that differs from the naturally occurring protein. The protein expressed by the minigene may have physiological effects, including toxic effects, that are not yet known. Because of the novelty of minigenes, the medical community's and regulators' receptiveness to this approach remains unknown. Our sponsored research may not fully elucidate all of the physiological risks associated with a particular minigene and the associated expressed protein. For these and other reasons, promising minigene candidates that emerge from our sponsored research programs with UMMS may not succeed in later stage preclinical and clinical development.

We have particularly focused on 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 that are associated with a number of diseases, such as LCA10, Stargardt disease and Usher 2A, exceed that size. Although AAV is the most commonly used vector in ocular gene therapy today, it may prove to pose safety risks that we are not aware of and 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 retinal drug development, our gene therapy research and development experience is limited to only a few personnel hired to supervise our outside service providers. In pursuing this new technology, we have begun to establish our own gene therapy technical capabilities, but we will need to continue to build those capabilities by either hiring internally or seeking assistance from 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 expand our gene therapy capabilities, we may not be able to develop in the way we intend or desire, IC-100, IC-200 or any promising product candidates that emerge from our miniCEP290 program or our other collaborative gene therapy sponsored research programs, which would limit our prospects for future growth.

We have not previously conducted any clinical development involving gene therapies. As we prepare for the potential initiation of our first gene therapy clinical trial, we will need to build our internal and external capabilities in designing and executing a gene therapy clinical trial. There are many known and unknown risks involved in translating preclinical development of gene therapies to clinical development, including selecting appropriate endpoints and dosage levels for dosing humans based on preclinical data. Furthermore, our gene therapy programs are targeting orphan diseases with relatively small populations, which limits the pool of potential subjects for our gene therapy clinical trials. Because gene therapy trials generally require subjects who have not previously received any other therapy for the same indication, we will also need to compete with our competitors who are also developing therapies for these same indications for the same group of potential clinical trial subjects. If we are unable to initiate and conduct our gene therapy clinical trials in a manner that satisfies our expectations or regulatory requirements, the value of our gene therapy programs may be diminished.

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*".

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 or identify a product candidate with a viable manufacturing process.

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, 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 process development and formulation development with our selected lead compound in this program to determine whether we can identify a viable manufacturing process for and formulate the lead compound for intravitreal administration that is safe to advance into preclinical studies and, depending on the outcome of such studies, into clinical trials. For example, as part of formulation development, 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. Process development and formulation development are inherently uncertain, and it is possible we may not be able to identify a viable manufacturing process for or formulate our lead compound or any backup compound 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. Manufacturing, including process development, and formulation development can be time-consuming and our anticipated timelines for the development of this program may be delayed.

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 preclinical studies or 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.

To date, we currently have safety data from a total of 113 patients receiving monthly treatments of either Zimura 2 mg or Zimura 4 mg for a minimum of 12 months in the OPH2003 trial. 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 data regarding the safety, tolerability or efficacy of Zimura administered for the treatment of STGD1. We have no human data regarding IC-100, IC-200 or any of our HtrA1 inhibitors.

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. For example, although the reduced rate of growth in GA we observed in the OPH2003 trial has not been associated with disproportionate loss of vision in the treated groups as compared to the sham control groups over the first 12 months of the trial, we may observe increased loss of vision in the Zimura treatment groups, as compared to the corresponding sham control arms, during the period between month 12 and month 18 in the trial or in the ISEE2008 trial. In addition, although we view the rate of CNV incidence in the Zimura treatment groups, as compared to the corresponding sham control groups, as acceptable and within the range observed in other clinical trials of complement inhibitors in development for GA, the FDA, EMA, other regulatory authorities, treating physicians or

patients may not agree, concluding that Zimura may increase the risk of patients developing CNV to an unacceptable degree. Moreover, our clinical trials for Zimura 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. For our OPH2003 trial, once all patients reach the 18 month time point, we expect that we will receive complete safety data, including unmasked data covering the period between month 12 and month 18. An unforeseen or unexpected safety issue, or any safety finding that is inconsistent with our prior experience with Zimura, including during the first 12 months of the OPH2003 trial, from any of our clinical trials for Zimura may impact our ability to continue to develop Zimura or the long-term viability of Zimura as a potential treatment for GA, STGD1 or any other indication for which we may seek to develop Zimura.

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. Managing 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 dispersal 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 retinal 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. 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 order to generate useful clinical data for gene therapy clinical trials, one or more retinal surgeon must repeat the same subretinal injection process in multiple patients with consistency across patients and surgeons. In addition, 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. In the event that we progress into clinical development with IC-100, IC-200 or any other gene therapy product candidate we may in-license or acquire, we may experience delays or other challenges for our gene therapy development programs as a result of safety issues.

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. The safety profile of minigenes and their associated proteins in humans remains largely unknown. 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. We may encounter manufacturing issues, including technical or quality issues, 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. If any of our product candidates is approved, a manufacturing issue could result in product shortages, which could impair our ability to commercialize our products and generate revenue.

We do not have internal manufacturing facilities and use or plan to use outside contract manufacturers to manufacture Zimura, IC-100, IC-200, our HtrA1 inhibitors 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. The manufacturing processes for our product candidates are technically complex. Problems with developing or executing 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, manufacturing and quality assurance and control 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. None of our third-party manufacturers have undergone a pre-approval inspection by the FDA for Zimura or any of our other product candidates. 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 collaborations, 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. As we plan for and conduct our ISEE2008 trial, we and our third-party manufacturers will need to complete several activities to ensure the continued supply of drug product for the trial and adequate preparations to support potential future commercial supply of Zimura. Any delay or failure in completing these activities could cause delays for the development of Zimura or its potential approval or could result in inadequate commercial product supply.

We currently use a single third-party manufacturer, Agilent, to supply us with the chemically synthesized drug substance for Zimura and a different, single third-party manufacturer, Ajinomoto, to provide fill/finish services for Zimura. We obtain the PEG reagent used to make Zimura API from a single third-party manufacturer. 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 our 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.

In early 2017, we completed the small scale manufacture of multiple batches of Zimura API that we plan to use to support clinical drug supply for the ISEE2008 trial. Although we believe we have adequate drug supply for the ISEE2008 trial, this supply may not be sufficient for our needs. We are in the process of recommencing manufacturing activities with our contract manufacturer, with the goal of scaling up and validating the manufacturing process to support the potential commercialization of Zimura. We will need to demonstrate that Zimura API produced through the scaled-up process is analytically comparable to the Zimura we are currently using before API manufactured through the scaled-up process can be used for commercial drug supply. We also plan to make a change to the vial used for the finished Zimura drug product during the course of the ISEE2008 trial in order to support a more robust fill/finish operation at commercial scale. These activities are costly, time-consuming and uncertain in outcome. We may not be able to successfully scale up or validate our manufacturing process for Zimura, demonstrate analytical comparability of the Zimura API manufactured through the scaled up process with the previously manufactured Zimura API, or establish the long-term stability of the finished Zimura drug product stored in the new vial container. We may need to perform additional work beyond what we currently plan to establish manufacturing and analytical capabilities sufficient to obtain regulatory approval of our manufacturing process for Zimura and to support potential

commercial operations. If any of the foregoing events occur, it could result in delays or increased costs to support our future development and commercialization of Zimura, even if we successfully complete any required clinical trials for Zimura and obtain sufficient and favorable safety and efficacy data.

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 certain other countries, do not apply to oligonucleotides, including aptamers. As a result, there are limited 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.

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 of which 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, any problems that arise during manufacturing, including during process development, may result in unanticipated delays to our timelines, including delays attributable to securing additional manufacturing time slots. There may also be long lead times to manufacture or procure starting materials such as plasmids and cell lines, especially for high-quality starting materials that are cGMP compliant. In particular, plasmids, cell lines and other starting materials for gene therapy manufacture are usually sole sourced, as there are a limited number of qualified suppliers. The progress of our gene therapy programs is highly dependent on these suppliers providing us or our contract manufacturers with the necessary starting materials that meet our requirements in a timely manner. 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 or quality issues for gene therapies, including raw material or starting material variability in terms of quality, cell line viability, productivity or stability issues, product and process impurities, shortages of any kind, shipping, distribution, storage and supply chain failures, growth media contamination, equipment malfunctions, operator errors, facility contamination, labor problems, natural disasters, disruption in utility services, terrorist activities, or acts of god that are beyond our or our contract manufacturer's control. It is often the case that early stage process development 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 particular, we and our contract manufacturers are developing our own manufacturing processes, which differ from those originally used by our university collaborators, for example, by using different starting materials. We may not be able to successfully translate the manufacturing process and our manufactured materials may not match the safety and efficacy profile of those used by the universities.

Because manufacturing for early stage research is often done under different conditions, using different starting materials and on a smaller scale than what is required for manufacturing for clinical supplies, we may face challenges in adapting the manufacturing processes that were used by our licensors and other academic collaborators and scaling up these processes as necessary to support supply for clinical trials. In order to progress the development of IC-100, IC-200 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.

An important part of manufacturing drug products is performing analytical testing. Analytical testing of gene therapies involves tests that are more numerous, more complex in scope and take a longer time to develop and to conduct as compared to those used for traditional drugs. We and our contract manufacturers need to expend considerable time and resources to develop assays and other analytical tests for our gene therapy product candidates, including assays to assess the potency of our gene therapy product candidates. Some assays need to be outsourced to specialized testing laboratories. Even when assays are developed, they need to be further tested, qualified and validated, which may take substantial time and resources. Because of the lagging nature of analytical testing, we may proceed with additional manufacturing and other development activities without having first fully characterized our manufactured materials. If the results of the testing fail to meet our expectations or applicable requirements, we may need to delay or repeat certain manufacturing and development activities.

We are only in the early stages of establishing manufacturing capabilities for our HtrA1 inhibitor program.

We have recently engaged a CDMO to conduct process development, scale-up and GMP manufacture of the API for the lead compound from our HtrA1 inhibitor program for potential preclinical toxicology studies and clinical trials. The time and efforts required for us to fully establish manufacturing capabilities for our HtrA1 inhibitor program, including developing a viable manufacturing process, if any, may delay or impair our ability to develop this program in accordance with our expected timelines.

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 and other programs from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies, as well as generic and biosimilar companies, worldwide. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. 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 product candidates that we may seek to develop or commercialize in the future.

We have recently transitioned to a business strategy that includes a focus on the development of gene therapies for orphan inherited retinal diseases. There are many companies pursuing gene therapy approaches for orphan and age-related retinal diseases. Some of them have better name recognition, more resources and a longer history of developing gene therapies than we do. Competition in this field is intense and for many inherited retinal diseases, there is a limited number of potential patients. If any of our competitors obtains FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, our competitors could establish a strong market position before we are able to enter the relevant market, which may significantly limit the commercial opportunity for our product candidates.

Our commercial opportunity could also 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. For example, the method of administration of Zimura, intravitreal injection, is commonly used to administer ophthalmic drugs for the treatment of severe diseases and is generally accepted by patients facing the prospect of severe visual loss or blindness. A therapy that offers a less invasive or less frequent method of administration, however, might have a competitive advantage over one administered by monthly intravitreal injections, depending on the relative safety of the other method of administration. 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 the IRDs for which we are researching and developing potential treatments, 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 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 development programs. Our timelines may be delayed to the extent clinical trials conducted by our competitors are enrolling patients that would otherwise be eligible to participate in our trials at the same time we are seeking to enroll these patients.

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 and clinical development by third parties to treat dry AMD or 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 complement system and inflammation suppression, visual cycle modulators, antioxidants and neuroprotectants, cell and gene therapies and vascular perfusion enhancers. We are aware that Apellis Pharmaceuticals, Inc., or Apellis, Roche AG, Novartis AG and MorphoSys AG, Hemera Biosciences, Inc., Gemini Therapeutics, Inc., NGM Biopharmaceuticals Inc., Gyroscope Therapeutics, Achillion Pharmaceuticals, Inc., and Biogen Inc. each have complement inhibitors in development for dry AMD, including, in the cases of Hemera Biosciences and Gyroscope Therapeutics, complement inhibitor gene therapies. We believe that the most advanced of these programs is Apellis's pegylated, synthetic peptide targeting complement protein C3. As recently as January 2020, Apellis confirmed its expectation that it would finish patient enrollment in its Phase 3 program during the early part of 2020 with the goal of enrolling approximately 1,200 patients, which would enable a primary 12-month efficacy analysis as early as the middle of 2021. If Apellis's Phase 3 program for its C3 complement inhibitor product candidate is successful, it is likely that Apellis would 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, including Allergan Inc., Allegro Ophthalmics, LLC, Alkeus Pharmaceuticals Inc., EyePoint Pharmaceuticals, Inc., Lineage Cell Therapeutics, Inc. and Stealth BioTherapeutics Corp, working in collaboration with Alexion Pharmaceuticals, Inc., are pursuing development programs for the treatment of dry AMD or GA using 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., Lin BioScience, Inc., Nightstar Therapeutics plc (prior to its acquisition by Biogen Inc.), ProQR Therapeutics N.V., Spark Therapeutics and Generation Bio Co. each have research or development programs in Stargardt disease. Three of these programs, Acucela, Alkeus 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:

- We are aware that ProQR Therapeutics N.V. is developing an RNA-based therapeutic for RHO-adRP, for which it has filed an IND and plans to enroll patients this year. We are also aware that multiple academic institutions have early stage gene therapy development programs in RHO-adRP. In addition, prior to its acquisition by Biogen Inc., Nightstar Therapeutics plc had a preclinical AAV gene therapy program in RHO-adRP. Sanofi is also exploring a potential program in this disease.

Competitive considerations for BEST1-related IRDs:

- We are aware that, prior to its acquisition by Biogen, Nightstar Therapeutics plc had a preclinical AAV gene therapy program for one or more *BEST1*-related IRDs.

Competitive considerations for LCA10:

- We are aware that Editas Medicine, Inc. (in partnership with Allergan plc) has a 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 late-stage clinical development, Generation Bio Co. has a preclinical program that utilizes ceDNA technology to target LCA10 and Oxford Biomedica plc is developing a lentiviral gene therapy program for LCA10 that is in preclinical development. In addition, several academic institutions have preclinical programs in LCA10.

Competitive considerations for USH2A-related IRDs:

- There are a number of products in preclinical research and clinical development by third parties to treat *USH2A*-related IRDs. We are aware that ProQR Therapeutics N.V. is pursuing two RNA based approaches for different mutations causing Usher 2A, one of which is currently in Phase 1/2 clinical development and the other of which is in preclinical development. We are also aware that Editas Medicine, Inc. and Odylia Therapeutics are exploring potential programs in *USH2A*-related IRDs.

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 or dedicated personnel. 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 indications for which the product candidate is approved, the territories 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. In contrast, our gene therapy programs are currently being developed for orphan IRDs with a limited number of affected individuals. If any of our product candidates is 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, if approved.

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 any 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 or with certain devices;
- any restrictions in the label on the use of our products by a subgroup of patients, including, for example, for our gene therapy product candidates, if approved, restrictions on use of our product if a patient previously received another gene therapy product;
- 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 frequent dosing regimen than monthly intravitreal injections, in the case of Zimura, or a less invasive method of administration than subretinal injection, in the case of our gene therapy product candidates, come to market. For example, Apellis is testing its complement inhibitor product candidate for GA with both monthly and every other month dosing regimens, and may obtain a label with an every other month dosing regimen, while we expect that any label we may obtain for Zimura in GA will require monthly administrations. If so, physicians and patients may find Apellis's dosing regimen more convenient than ours.

Our development program for Zimura in GA uses an anatomical primary endpoint, the mean rate of change in GA growth. We believe that this efficacy assessment is most likely to demonstrate clinical relevance for an investigational product across a heterogeneous GA patient population and other potential assessments, such as comparisons of visual acuity, are not as clinically meaningful for patients with GA. However, to date there is no direct functional corollary to the anatomical measure that we are using as our primary endpoint. Although we evaluated vision as a secondary endpoint in the OPH2003 trial, the trial was not designed to reliably assess differences in mean changes in vision with statistical significance. Patients, physicians and payors may not recognize the value of, and we may not be able to obtain marketing or reimbursement approval for, Zimura without demonstrating a functional benefit to vision. To do so, we may need to conduct additional clinical trials, which may not ultimately demonstrate a functional benefit to vision.

For each of our Zimura trials where patients receive multiple intravitreal injections on the same day, we have provided for a delay in the second intravitreal injection to occur during the same office visit to minimize the risk of an unacceptable increase in intraocular pressure as a result of the volume of the multiple injections. 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, the expected patient population for our product candidates, our industry knowledge, the competitive landscape for the indications for which we are developing our product candidates and programs, market response to Spark Therapeutics's Luxturna®, Novartis AG's Zolgensma® and anti-VEGF agents currently approved for treatment of wet AMD, 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.

There is a variety of factors that could contribute to the actual number of patients who receive an approved therapy being less than our estimates of the potential addressable market. 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, patients may not be 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. Further, the severity of the progression of a disease up to the time of treatment, especially in certain degenerative conditions such as IRDs, likely will diminish the therapeutic benefit conferred by a gene therapy due to irreversible cell death. Certain patients' immune systems and prior exposure to the virus used to deliver a gene therapy might inhibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting eligibility for treatment or limiting treatment outcomes. If the number of patients that may benefit from the treatments we are seeking to develop is lower than we expect, our business, financial condition, results of operations and prospects may be adversely affected.

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. Many countries outside the United States require approval of the sale price of a drug before it can be marketed, and to apply for and obtain such an approval in certain 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. 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. In particular for Zimura in GA, we may need to demonstrate visual function in order to obtain reimbursement approval, although our clinical trials, which use an anatomic endpoint as the primary efficacy endpoint, are not designed to demonstrate a functional benefit with statistical significance. 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, which would 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 are only two FDA-approved gene replacement therapy products, both of which launched in the United States within the past two years, 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 may not be realized or are realized over a period of years during which the patient may no longer be enrolled in the payor's plan. Although payors and manufacturers may be incentivized to agree to outcomes-based payment structures for gene therapies, where manufacturers provide rebates or a portion of the contract price is forgiven if an efficacy or durability threshold is not met for an individual patient, market dynamics in the United States currently do not facilitate these types of outcome-based payments, in particular because of rules that require that government payors, such as Medicaid, receive the "best price" for a drug, regardless of outcome. The perceived high cost for pharmaceutical products to treat orphan diseases, where manufacturers seek to recoup development costs and earn a profit for a therapy intended to treat a relatively small patient population, may attract increased political and public scrutiny. In particular, the $2.1 million list price for Zolgensma has generated significant public scrutiny over the prices of new pharmaceuticals coming to the market, including gene therapies, and as a result, Novartis has proposed permitting third-party payors to pay for Zolgensma in annual installments over five years instead of as a lump sum. 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 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, through the Center for Medicare & Medicaid Service, or CMS, announced in late 2018 an advance notice of proposed rulemaking describing a potential mandatory reference pricing model for Medicare Part B drugs under which the prices paid for these drugs will be adjusted in relation to an international pricing index that includes prevailing prices from other countries with strict price controls. CMS is considering issuing a proposed rule that would describe the model in more detail, with the goal of starting the model in spring 2020. The Trump Administration has also expressed an interest in authorizing and/or directing CMS 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 pharmaceutical 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 at 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. For example, several insurers have limited the subpopulation for or imposed additional eligibility criteria for paying for Zolgensma, beyond the requirements of the approved FDA label, such as requiring that any eligible patients must receive another treatment first and demonstrate that the other treatment is ineffective before using Zolgensma. 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 and certain members of the U.S. Congress have 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.

For a further discussion of health care reform and other political factors affecting drug prices, see the risk factor herein entitled "*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 charge for such products, when and if approved.*"

Ethical, legal and social issues related to genetic testing may reduce demand for any gene therapy product candidates we develop and for which we seek marketing approval.

We anticipate that prior to receiving certain gene therapies, including as part of a clinical trial, patients would be required to undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. The ownership of genetic data is an area of the law that is unclear and varies across jurisdictions. Genetic tests for assessing a person's likelihood of developing a chronic disease have focused public attention on the need to protect the privacy of genetic information. For example, concerns have been raised that insurance carriers and employers may use these tests to discriminate on the basis of genetic information, resulting in barriers to

the acceptance of genetic tests by consumers. This dynamic could lead to governmental authorities restricting genetic testing or calling for limits on or regulating the use of genetic testing, particularly for diseases for which there is no known cure, as well as the use of genetic data. Any of these scenarios could decrease the pool of patients willing to participate in a clinical trial for a gene therapy and the demand for a gene therapy once it is approved.

The novel coronavirus outbreak that began in Wuhan, China may affect our ability to recruit or retain patients for our clinical trials, disrupt our supply chains or have other adverse effects on our business and operations.

In December 2019, an outbreak of respiratory illness caused by a novel coronavirus began in Wuhan, China. As of February 2020, that outbreak has lead to tens of thousands of confirmed cases worldwide, with many countries throughout the world confirming cases. The World Health Organization has declared the outbreak a global public health emergency. In addition to those who have been directly affected, millions more have been affected by government efforts in China and around the world to slow the spread of the outbreak through quarantines, travel restrictions, heightened border scrutiny and other measures. The outbreak and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. The future progression of the outbreak and its effects on our business and operations are uncertain. We seek to enroll patients for our clinical trials at sites located both in the United States and internationally. We may face difficulties recruiting or retaining patients in our ongoing and planned clinical trials if patients are affected by the virus or are fearful of traveling to our clinical trial sites because of the outbreak. We and our third-party contract manufacturers, contract research organizations and clinical sites may also face disruptions in procuring items that are essential for our research and development activities, including, for example, raw materials used in the manufacture of our product candidates, medical and laboratory supplies used in our clinical trials or preclinical studies or animals that are used for preclinical testing, in each case, that are sourced from abroad or for which there are shortages because of ongoing efforts to address the outbreak.

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, including coverage for any local jurisdictions where we conduct clinical trials. 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 product candidates of sufficient quality, 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. Although we plan to enter into a long-term clinical and commercial supply agreement with our third-party manufacturer, we do not currently have any contractual commitments for the supply of Zimura drug substance and we may not be able to come to agreement with our third-party manufacturer for a long-term clinical or commercial supply agreement. 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.

We have engaged a gene therapy CDMO for preclinical and Phase 1/2 clinical supply of IC-100 and IC-200. For our HtrA1 inhibitor program, we have recently engaged a CDMO to conduct process development, scale-up and GMP manufacture of the API of our lead compound for potential preclinical toxicology studies and clinical trials.

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.

Our third-party manufacturer for the API for Zimura and our CDMO for IC-100 and IC-200 are currently undergoing rapid expansion, including ramping up for production for existing clients, bringing on additional clients, opening new facilities, installing and validating new equipment, and hiring and training new personnel. Their expansion, including any issues that they may experience while expanding, could affect the timing, costs, progress, quality and outcome of our planned manufacturing activities with those manufacturers and delay or hinder our development plans.

If any of our third-party manufacturers, fill/finish providers or sole-source suppliers fail to fulfill our contracts or 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 activities.

We are relying upon and expect in the future to rely upon third parties, such as contract research organizations, or CROs, clinical data management organizations, biostatisticians, medical institutions (including reading centers) and clinical investigators, in conducting our preclinical testing and clinical trials for our product candidates. These third parties may also have relationships with other entities, some of which may be our competitors. 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.

We also rely upon our university collaborators to conduct some of our preclinical studies. In particular, Penn has the canine disease model for two of the diseases we are aiming to treat: RHO-adRP and *BEST1*-related retinal diseases. Our preclinical development plans for both IC-100 and IC-200 include conducting certain preclinical studies using the associated canine disease models. If the canines that we are intending to use are not available to us for any reason, our development of IC-100 or IC-200 could potentially be delayed or otherwise adversely affected.

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.

Over the past few years, there has been increasing oversight by the FDA and other regulatory authorities on data integrity, especially in the research and development of novel therapies such as gene therapies. We rely upon the practices of and systems in place at our third party collaborators in generating data to support our preclinical and clinical development programs and for quality control over this data. Their practices and systems vary in scope and effectiveness and we have a limited number of personnel to supervise, including to perform quality assurance of, those practices and systems. Any failure of such practices or systems to comply with our stated protocols or regulatory requirements could adversely affect the quality of the data generated by these studies. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or 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.

We also rely upon other third parties to store, package, label and distribute drug supplies for our clinical trials and to store materials for our development activities. In particular, we rely on a limited number of third parties to store starting materials, drug substance and drug product for our product candidates and programs. Any performance failure on the part of these third parties could delay preclinical development, clinical development or marketing approval of our product candidates or commercialization of our products and adversely affect our results of operations.

We rely upon 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. The sponsored research agreements we enter into for these programs generally provide that any inventions resulting from the research will be owned by the research institution performing the research, and that we have an option to negotiate for a license to develop and exploit any such inventions. Confidential information and new inventions derived from these research efforts may be disclosed through publications or other means prior to our third-party research collaborators being able to protect such intellectual property through the filing of patent applications. Our third-party research collaborators 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 seek to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates. In particular, we continue to explore potential collaboration opportunities for the further development and potential commercialization of Zimura.

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. For our gene therapy programs, we are party to in-license agreements that limit who we can collaborate with or require the approval of our licensor for us to enter into a collaboration, and any future license agreements that we may enter into may have similar restrictions. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among pharmaceutical and biotechnology 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 those product candidates or bring them to market and generate product revenue.

If we enter into collaborations with third parties for the development or commercialization of our product candidates, any such collaborations will 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 develop or 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, including marketing and distribution 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 of our 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;
- laws or practices in certain foreign jurisdictions may require that as a condition of working with a collaborator in such jurisdiction, we agree to certain foreign ownership restrictions, use certain local services or providers, share or license certain of our proprietary information or technology or other conditions that are not attractive to us; 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 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, IC-100, IC-200 and our miniCEP290 program. 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 or technologies. 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. We are party to two different license agreements, each with UFRF and Penn, on which we depend for rights to IC-100 and IC-200. We are also party to a license agreement with UMMS for our miniCEP290 program. 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 specified diligence and milestone payment obligations on us. We may enter into acquisition or licensing agreements in the future that would impose similar obligations on 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, IC-100, IC-200, our miniCEP290 program, 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 the relevant 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 agreements for IC-100, IC-200 and our miniCEP290 program reserve 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 candidates, separate from our research and development efforts, that is inconsistent with other data for such product candidates, 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 candidates 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, 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.

We currently rely and expect to continue to rely on patent rights to protect our competitive position. Once our patents expire, we may not be able to exclude competitors from commercializing products similar or identical to ours. 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. We expect the clinical development of Zimura to continue for at least the next several years. If so, the patents covering Zimura may expire before the date by which we or a potential commercial partner would be able to commercialize Zimura in the United States or Europe if we seek and obtain marketing approval. 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 the patent rights under existing patent applications for IC-100, our miniCEP290 program and our HtrA1 inhibitors are not expected to expire until 2037 or after, we face the same risk with those product candidates and programs and any future product candidates that we may develop.

Our product candidate IC-200 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.

Certain of our licensed patent rights for Zimura and IC-100 are method-of-treatment patents and patent applications. 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 they 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.

Depending on potential delays in the regulatory review process for any of our product candidates, 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 commercialize competing products following our patent expiration, and our revenue could be reduced, possibly materially.

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.

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.

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 or biosimilar 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 or biosimilar 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 may 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.

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. The Leahy-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. 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 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. For some of our licensed patent rights, we may need the cooperation of our licensors to file such claims. 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 increase as our product candidates near commercialization.

Third parties may assert infringement or other 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. In addition, contract manufacturers may inadvertently incorporate intellectual property belonging to third parties into our products or the manufacturing processes for these products without our knowledge. 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 product candidates or products 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 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 or contractors 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' 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 sooner than we expect, which would have a material adverse effect on our business.

In addition, we may decide not to pursue patent prosecution in certain major markets or jurisdictions. For example, we may decide that the costs of obtaining and maintaining patent protection in a certain jurisdiction may outweigh the commercial benefits of patent protection. If so, our competitors may enter into and commercialize identical or similar products in that jurisdiction and if we choose to commercialize our products in that jurisdiction, we may not be able to exclude our competitors in the same way as if we had chosen to pursue patent prosecution in that jurisdiction.

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 outside scientific collaborators, contract manufacturers, potential business development counterparties, 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 our HtrA1 inhibitor program through the acquisition of Inception 4, we are relying upon Inception 4's, and its prior owner'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 and 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 information relating to our business and that of our clinical trial participants, business collaborators and employees. In particular, we rely on contract research organizations and other third parties to store and manage data generated from our preclinical research and development activities and 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 incidents, 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. 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 could be damaged.

A data security breach could also lead to public or unauthorized exposure of personal information of our clinical trial participants, 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 collaborators 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 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 data 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. We are aware that several states have enacted or are considering legislation similar to the GDPR. 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 setbacks in the development or approval of our product candidates, 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 and import and export, are subject to comprehensive regulation by the FDA, 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 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 and our gene therapy product candidates 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 two gene replacement products 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. The approval requirements in foreign jurisdictions may differ significantly from those in the United States.

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 marketing and/or reimbursement 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.

In June 2016, the electorate in the United Kingdom, or UK, voted in favor of leaving the European Union, commonly referred to as "Brexit". Following protracted negotiations, the UK left the European Union on January 31, 2020. There is a transitional period until December 31, 2020, and the UK government and the European Union are attempting to agree to long-term trade and other agreements. Since the existing regulatory framework for pharmaceutical products in the UK is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime for pharmaceutical products in the UK, which remains uncertain. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

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 product candidate is eligible for such designation or status the FDA could decide not to grant it. Even though a product candidate 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 Drug 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 decide 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 ensure 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 that the time period for FDA review or approval will not be shortened.

We currently do not have orphan drug designations or orphan drug exclusivity for any product candidate. 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 our product candidates 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 during that marketing exclusivity period from approving another marketing application for a product that constitutes the same drug treating the same indication, 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 candidate during 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 later 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 remains in flux in the context of gene therapies, and the FDA has issued recent draft guidance suggesting that it would not consider two gene therapy products to be different drugs solely based on minor differences in the transgenes or vectors. 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 the orphan medicinal product.

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 the continued 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 FDCA 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;
- 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.

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 a minimum of $11,181 and a maximum of $22,363 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 certain manufacturers of drugs, medical devices and biological products covered by federal healthcare benefit programs to report payments and other transfers of value to physicians and teaching hospitals; 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 governmental and 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, such as the 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.

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. As our product candidates advance in clinical development, we plan to develop and implement a corporate compliance program to ensure that we will market and sell any future products that we successfully develop in compliance with all applicable laws and regulations, but we cannot guarantee that any such program will protect us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws and 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, including 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.

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 charge for such products, when and if approved.

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 charge 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, originally 50% and as of 2019, 70%, 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 TCJA, Congress repealed the "individual mandate." The repeal of this provision, which required most Americans to carry a minimal level of health insurance, became 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. Further, the Bipartisan Budget Act of 2018, among other things, amended 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 amend or replace 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, which has lead to numerous legal challenges to the ACA and the Trump Administration's actions. Since January 2017, President Trump has signed at least 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. A second executive order terminated the cost-sharing subsidies that reimburse insurers under the ACA, which has lead some states attorneys general and some insurers to sue the Trump Administration for such payments and a number of those lawsuits remain pending. 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, which the U.S. Supreme Court is reviewing during its current term. In addition, in October 2018 CMS promulgated 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. Additional executive actions or regulations may be forthcoming.

In addition, in December 2018, a U.S. District Court in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The Trump Administration and CMS have both stated that the ruling will have no immediate effect, and later in December 2018, the same court issued an order staying the judgment pending appeal. In December 2019, the U.S. Circuit Court of Appeals for the Fifth Circuit affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. In January 2020, the U.S. Supreme Court declined to review this decision on an expedited basis.

We will continue to evaluate the effect that the ACA, its possible amendment or repeal and the actions of the Trump Administration in relation to the ACA could have on our business. It is possible that amendment or repeal 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 amend or repeal ACA provisions is highly uncertain in many respects, including the possibility that any such amendment or repeal is brought about by a court ruling rather than legislative action, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be amended or repealed.

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. In September 2019, members of both houses of Congress unveiled separate bills aimed at controlling drug pricing. At the state level, individual states are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing and to increase the transparency of drug 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, if approved.

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 commercialization of our product candidates, if any, may be.

Our operations may be dependent on the normal function of 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 product applications such as INDs, new drug applications and biologics license applications 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.

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. International Travel Act of 1961, 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 and any coverage provided by our insurance. 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 product candidates or 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 to oversee our research and development programs and general and administrative functions. We may experience difficulties in recruiting necessary personnel, especially in building our gene therapy capabilities, and in retaining key employees and consultants.

We are a development-stage company with a total of 38 full-time employees as of January 31, 2020. These employees support key areas of our business and operations, including clinical operations, regulatory affairs, drug safety, data management, medical affairs, 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 whom we expect to retain to assist with the growth of our business may choose not to remain employees. Additionally, because of our size, we have only a small number of employees supporting some of the key areas of our business and operations. If any of those employees were to leave our company, the loss of their services could seriously disrupt our ability to carry on our operations as planned and seriously harm our ability to successfully implement our business plan.

Furthermore, replacing any of our 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. In preparation for our ISEE2008 trial and future development and potential commercialization of Zimura, we expect we will need to hire additional clinical operations, manufacturing, medical, regulatory and other personnel from this limited pool. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions.

In addition to our employees, 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. 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. Many consultants and advisors, especially those with gene therapy experience, are high demand and we may not be able to obtain or retain their services for any number of reasons, which could limit our ability to pursue our strategy.

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 any 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 our 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:

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

Following periods of volatility in the market price of a company’s stock, securities class-action litigation has often been instituted against that company. For example, we and certain of our current and former executive officers have been named as defendants in a purported class action lawsuit and a related shareholder derivative action 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. For example, we issued 5,174,727 shares of our common stock to the former equityholders of Inception 4 as upfront consideration for our acquisition of Inception 4. These shares were subject to lock-up restrictions, which expired 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 pursuant to a registration statement on Form S-3 (File No. 333-229978) that was declared effective by the Securities and Exchange Commission on April 25, 2019. If the holders of these shares sell, or the market perceives that these holders will sell, the shares currently held by them, the price of our common stock may decline.

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.

The ownership percentage of our stockholders may be diluted in the future, which could dilute the voting power or reduce the value of our outstanding shares of common stock.

As with any publicly traded company, the ownership percentage of our stockholders may be diluted in the future because of equity issuances for acquisitions, capital markets transactions, business development transactions or otherwise, including equity awards that we intend to continue to grant to our directors, officers and employees pursuant to our equity compensation plans. Our employees are also entitled, subject to certain conditions, to purchase our ordinary shares at a discount pursuant to our Employee Stock Purchase Plan.

In addition, the warrants that we issued in connection with our December 2019 public offering are exercisable at any time, and any exercise of such warrants will increase the number of shares of our outstanding common stock, which may dilute the ownership percentage or voting power of our stockholders.

Also, our certificate of incorporation authorizes us to issue, without the approval of our shareholders, one or more classes or series of preferred stock having such designation, powers, preferences and relative, participating, optional and other special rights, including preferences over our common stock with respect to dividends and distributions, as our board of directors generally may determine. The terms of one or more classes or series of preferred stock could dilute the voting power or reduce the value of our ordinary shares. Similarly, the repurchase or redemption rights or liquidation preferences we could assign to holders of preferred stock could affect the residual value of our common stock.

For more information about the dilutive effects of financing or business development transactions we may undertake, see the risk factor above, "*Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates*."

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 of our business. In addition, the terms of any future debt agreements that we enter into 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 material properties consist of approximately 13,500 square feet of office space in New York, New York, which we rent pursuant to a lease that is scheduled to expire at the end of June 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. On September 18, 2019, the court issued an order dismissing some, but not all, of the allegations in the CAC. On November 18, 2019, we and the individual defendants filed an answer to the complaint. This case is currently in the discovery phase.

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 our board of directors relative to boards of directors 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. The court approved the settlement at a hearing on March 12, 2019. As part of the settlement, in April 2019 we paid $300,000 in fees and costs to plaintiff's counsel. As contemplated by the settlement, our board adopted certain compensation-related governance reforms, including a non-employee director compensation policy, which our stockholders approved on May 15, 2019 at our 2019 annual meeting.

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. On September 19, 2019, the court denied our motion to dismiss this complaint. This matter was subsequently referred to a special litigation committee of our board of directors. On February 18, 2020, we filed an answer to the complaint.

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. These shareholder demands have been referred to a demand review committee of our board of directors.

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" from September 25, 2013 to April 16, 2019, and under the symbol "ISEE" since April 17, 2019.

Holders

As of January 31, 2020, there were approximately 98 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

In July 2019, we issued to the University of Massachusetts 75,000 shares of our common stock as upfront consideration for the exclusive license agreement for our miniCEP290 program. Based on and relying on certain representations made by the University of Massachusetts, we issued these shares pursuant to an exemption from registration afforded by Section 4(a)(2) of the Securities Act. The foregoing transaction did not involve any underwriters, underwriting discounts or commissions, or any public offering.

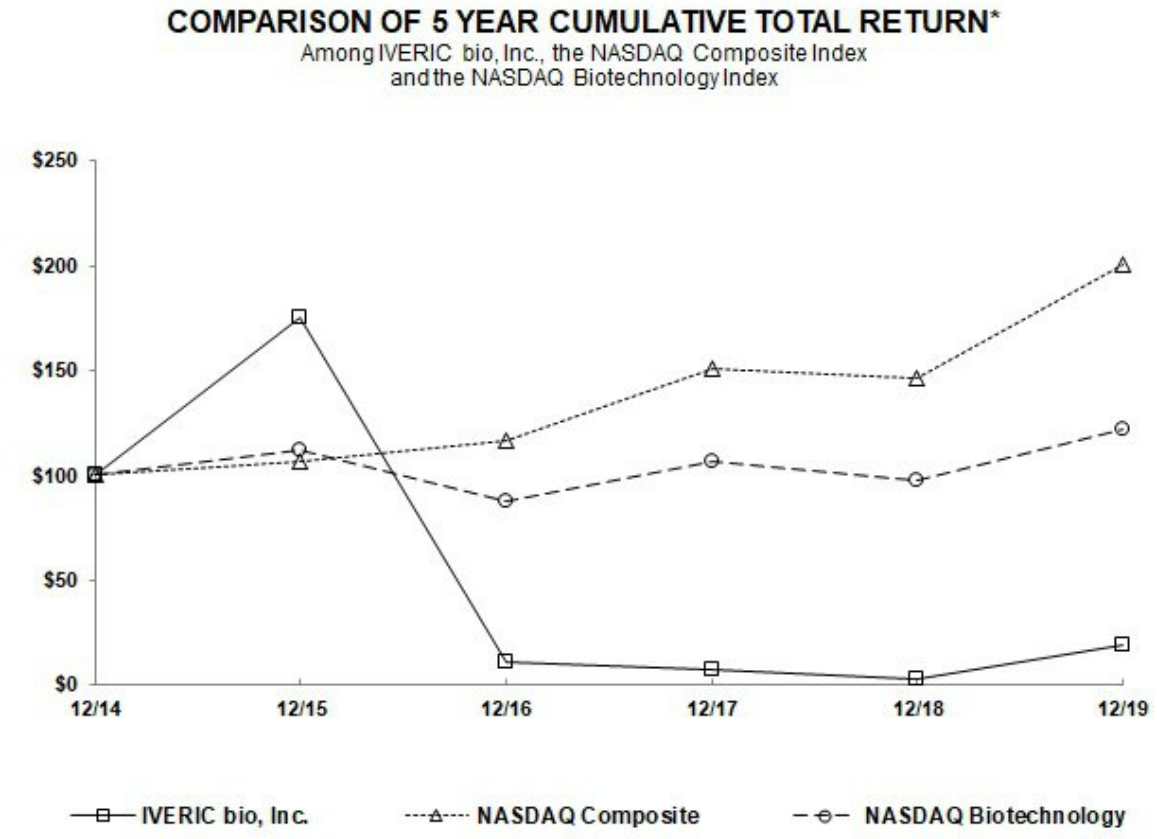
Except for the foregoing, there were no issuances of equity securities that were not registered under the Securities Act during the period covered by this Annual Report on Form 10-K.

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, 2014 and ending on December 31, 2019, to that of the total return for the NASDAQ Composite Index and the NASDAQ Biotechnology Index, assuming an investment of $100 on December 31, 2014. 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.



	12/14	12/15	12/16	12/17	12/18	12/19
IVERIC bio, Inc.	$ 100.00	$ 175.02	$ 10.76	$ 6.95	$ 2.67	$ 19.12
NASDAQ Composite	100.00	106.96	116.45	150.96	146.67	200.49
NASDAQ Biotechnology	100.00	111.77	87.91	106.92	97.45	121.92

*$100 invested on December 31, 2014 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, 2019, 2018, 2017, 2016 and 2015 and the balance sheet data as of December 31, 2019, 2018, 2017, 2016 and 2015 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,				
	2019	2018	2017	2016	2015
	(in thousands, except per share data)				
Statements of Operations Data:					
Collaboration revenue	$ —	$ —	$ 209,977	$ 50,909	$ 51,505
Operating expenses:					
Research and development	39,644	41,737	66,289	196,295	131,012
General and administrative	21,628	23,612	35,683	50,178	44,021
Total operating expenses	61,272	65,349	101,972	246,473	175,033
Income (loss) from operations	(61,272)	(65,349)	108,005	(195,564)	(123,528)
Interest income (expense)	2,151	2,389	1,522	1,704	971
Gain on extinguishment of royalty purchase liability	—	125,000	—	—	—
Other income (expense)	151	(16)	(34)	34	53
Income (loss) before income tax provision (benefit)	(58,970)	62,024	109,493	(193,826)	(122,504)
Income tax provision (benefit)	(111)	(1,063)	(4,712)	(406)	(16,787)
Net income (loss)	$ (58,859)	$ 63,087	$ 114,205	$ (193,420)	$ (105,717)
Net income (loss) per common share:					
Basic	$ (1.39)	$ 1.70	$ 3.18	$ (5.45)	$ (3.06)
Diluted	$ (1.39)	$ 1.70	$ 3.17	$ (5.45)	$ (3.06)
Weighted average common shares outstanding:					
Basic	42,224	37,061	35,919	35,486	34,580
Diluted	42,224	37,088	36,007	35,486	34,580

	As of December 31,				
	2019	2018	2017	2016	2015
	(in thousands)				
Balance sheets data:					
Cash, cash equivalents, and marketable securities	$ 125,699	$ 131,201	$ 166,972	$ 289,278	$ 391,890
Total assets	$ 130,187	$ 137,165	$ 175,576	$ 299,630	$ 428,851
Deferred revenue	$ —	$ —	$ —	$ 209,976	$ 213,066
Royalty purchase liability	$ —	$ —	$ 125,000	$ 125,000	$ 125,000
Total liabilities	$ 12,984	$ 13,206	$ 137,535	$ 394,248	$ 368,904
Additional paid-in capital	$ 597,679	$ 545,585	$ 522,759	$ 504,517	$ 465,927
Accumulated deficit	$(480,526)	$(421,667)	$(484,754)	$(598,959)	$(405,539)
Total stockholders' equity (deficit)	$ 117,203	$ 123,959	$ 38,041	$ (94,618)	$ 59,947

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 focused on the discovery and development of novel treatment options for retinal diseases with significant unmet medical needs. We are currently developing both therapeutic product candidates for age-related retinal diseases and gene therapy product candidates for orphan inherited retinal diseases, or IRDs. In April 2019, we changed our name from Ophthotech Corporation to IVERIC bio, Inc. as we continued to broaden the focus of our company to include gene therapies.

We believe that both therapeutics and gene therapy serve important roles in drug development and providing potential treatment options for patients suffering from retinal diseases. Our most advanced therapeutic product candidate is Zimura® (avacincaptad pegol), a complement C5 inhibitor. In October 2019, we announced initial, top-line data from a randomized, controlled clinical trial of Zimura in geographic atrophy, or GA, secondary to dry age-related macular degeneration, or AMD, which we will refer to as the OPH2003 trial. The top-line data confirmed that Zimura met the prespecified primary endpoint in the trial in reducing the rate of GA growth in patients with dry AMD. The reduction in the mean rate of GA growth over 12 months using the square root transformation was 0.110 mm (p-value = 0.0072) for the Zimura 2 mg group as compared to the corresponding sham control group and 0.124 mm (p-value = 0.0051) for the Zimura 4 mg group as compared to the corresponding sham control group, indicating an approximate 27% relative reduction in the mean rate of GA growth over 12 months when compared with sham for both dose groups. These data for both dose groups were statistically significant and we believe demonstrate a clinically relevant reduction in rate of GA growth. Based on our review of the safety data to date, Zimura was generally well tolerated over 12 months of administration in this clinical trial. Over this 12-month period, there were no investigator-reported ocular serious adverse events, no Zimura-related adverse events, no cases of Zimura-related intraocular inflammation, no cases of Zimura-related increased intraocular pressure, no cases of endophthalmitis, and no discontinuations attributed by investigators to Zimura. OPH2003 was designed to be a Phase 2b screening trial, with the potential to qualify as a pivotal trial depending on the magnitude and statistical significance of the potential benefit observed. We believe that the safety and efficacy results from the OPH2003 trial could potentially satisfy the U.S. Food and Drug Administration's, or FDA's, requirements as one of the two pivotal clinical trials typically required for marketing approval of a pharmaceutical product. We are preparing for an international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial of Zimura in this indication, which we refer to as the ISEE2008 trial, with the goal of beginning patient enrollment during the first quarter of 2020.

We currently have two gene therapy product candidates in preclinical development and several collaborative gene therapy sponsored research programs ongoing. Subject to successful completion of preclinical development and manufacturing under current good manufacturing practices, or GMP, and regulatory review, we plan to initiate a Phase 1/2 clinical trial for IC-100, our lead gene therapy product candidate, during the fourth quarter of 2020.

Our therapeutics portfolio consists of Zimura and our preclinical development program of High temperature requirement A serine peptidase 1 protein, or HtrA1, inhibitors. We are targeting the following diseases with Zimura:

- GA, which is the advanced stage of AMD, and is characterized by marked thinning or atrophy of retinal tissue, leading to irreversible loss of vision; and
- autosomal recessive Stargardt disease, or STGD1, which is characterized by progressive damage to the central portion of the retina, or the macula, and other retinal tissue of young adults, leading to 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, which we refer to as the OPH2007 trial, during the fourth quarter of 2018. We are developing our HtrA1 inhibitor program for GA and potentially other age-related retinal diseases.

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;
- IRDs associated with mutations in the *BEST1* gene, including Best vitelliform macular dystrophy, or Best disease, which is generally characterized by bilateral egg yolk-like lesions in the macula, which, over time, progress to atrophy and loss of vision;
- Leber Congenital Amaurosis type 10, or LCA10, which is characterized by severe bilateral loss of vision at or soon after birth;
- autosomal recessive Stargardt disease; and
- IRDs associated with mutations in the *USH2A* gene, which include Usher syndrome type 2A, or Usher 2A, and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa.

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 and are planning an additional, Phase 3 clinical trial for Zimura. The following is a brief description of these trials and their current status:

- **OPH2003 (GA secondary to dry AMD)**: an ongoing international, randomized, double masked, sham controlled, multi-center pivotal clinical trial evaluating the safety and efficacy of various doses of Zimura in patients with GA secondary to dry AMD. We enrolled a total of 286 patients in this trial. In October 2019, we announced initial, top-line data from this trial based on the first 12 months of this trial. This trial remains ongoing and, in accordance with the clinical trial protocol, patients will continue to be treated and followed through month 18. The primary purpose of the 18 month time point is to gather additional safety data. This trial is not designed to assess, and the prespecified statistical analysis plan for the trial does not include assessing, the statistical significance of the 18 month efficacy data for the treatment groups as compared to the corresponding sham control groups. Any analysis of the 18-month efficacy data will be descriptive only. We expect the month 18 data to be available by the end of the second quarter of 2020.

- **ISEE2008 (GA secondary to dry AMD):** a planned international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial evaluating the safety and efficacy of Zimura 2 mg in patients with GA secondary to dry AMD. The primary efficacy endpoint for this trial will be the same as the primary efficacy endpoint for the OPH2003 trial, and, if data from this trial are positive, we expect this trial to potentially qualify as a second, pivotal clinical trial that may provide data, together with the data from our other Zimura clinical trials, to support a marketing application for Zimura in GA. We plan to enroll approximately 400 patients in this trial, with the goal of beginning patient enrollment during the first quarter of 2020.

- **OPH2005 (STGD1)**: an ongoing, randomized, double masked, sham controlled, multi-center Phase 2b clinical trial, which we refer to as the OPH2005 trial, evaluating the safety and efficacy of Zimura for the treatment of STGD1. Similar to OPH2003, OPH2005 was designed to be a Phase 2b screening trial, with the potential to demonstrate statistically significant results depending on the magnitude of the potential benefit observed, and which we believe could potentially serve as a pivotal clinical trial. We completed enrollment for this 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 our HtrA1 inhibitor program for the treatment of GA secondary to dry AMD and potentially other age-related retinal diseases. Our HtrA1 inhibitor program includes a number of small molecule compounds that show high affinity and specificity for HtrA1 when tested. We have identified a lead compound from this

program. We are pursuing process development and formulation development with the goal of developing a manufacturing process and a formulation for intravitreal administration of this lead compound in the eye. If we are successful in developing a manufacturing process for and formulating this lead compound, we plan to initiate investigational new drug, or IND, enabling activities for this product candidate. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing, we plan to file an IND for a product candidate from this program during 2021.

Gene Therapy Research and Development Programs

IC-100: Product Candidate for RHO-adRP

We are pursuing the preclinical development of IC-100, 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 preclinical studies of IC-100 and a natural history study of RHO-adRP patients. In parallel, 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 IC-100. We are conducting Phase 1/2 clinical manufacturing and other IND-enabling activities. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing and regulatory review, we plan to initiate a Phase 1/2 clinical trial for IC-100 during the fourth quarter of 2020.

IC-200: Product Candidate for BEST1-Related IRDs

We are pursuing the preclinical development of IC-200, our novel AAV gene therapy product candidate for the treatment of *BEST1*-related IRDs, including Best disease, to which we acquired exclusive development and commercialization rights through an April 2019 license agreement with Penn and UFRF. We and Penn are conducting preclinical studies of IC-200 and natural history studies of patients with *BEST1*-related IRDs. In parallel, we have engaged a gene therapy CDMO as the manufacturer for preclinical and Phase 1/2 clinical supply of IC-200. We are planning for Phase 1/2 clinical manufacturing and other IND-enabling activities. Based on current timelines and subject to successful completion of preclinical development and GMP manufacturing and regulatory review, we expect to initiate a Phase 1/2 clinical trial for IC-200 during the first half of 2021.

Minigene Programs

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 goal of minigene therapy is to deliver a gene expressing a protein that, although different from the naturally occurring protein, is nonetheless functional for purposes of treating the associated disease.

We are funding several sponsored research programs at UMMS seeking to use a minigene approach to develop new gene therapies for several orphan IRDs. The following is a summary of these minigene programs and their status:

- **miniCEP290 (LCA10):** This program, which we refer to as the miniCEP290 program, is targeting LCA10, which is associated with mutations in the *CEP290* gene. In July 2019, we entered into a license agreement with the University of Massachusetts, or UMass, for exclusive development and commercialization rights to this program. The sponsored research, which is ongoing, has yielded a number of minigene constructs that show encouraging results when tested in a mouse model. UMMS is continuing to optimize constructs with the goal of identifying a lead construct by the middle of 2020.

- **miniABCA4 (STGD1):** This program, which we refer to as the miniABCA4 program, is targeting STGD1, which is associated with mutations in the *ABCA4* gene. UMMS has generated and is evaluating several *ABCA4* minigene constructs in both *in vitro* and *in vivo* experiments. We have received preliminary results and expect to receive additional results from the miniABCA4 program during the second half of 2020.

- **miniUSH2A (*USH2A*-related IRDs):** This program, which we refer to as the miniUSH2A program, is targeting IRDs associated with mutations in the *USH2A* gene, including Usher 2A and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa. We initiated this sponsored research with UMMS in July 2019 and expect to receive preliminary results during the second half of 2020.

In addition to the license agreement for the miniCEP290 program, 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.

Business Development and Financing Activities

Since early 2017, we have been pursuing a business development strategy to evaluate available technologies to treat ophthalmic diseases, particularly those in the back of the eye, and to explore opportunities to obtain rights to additional products and product candidates employing these technologies. As we evaluated numerous potential opportunities, we have come to believe that gene therapy, in addition to therapeutics, is a promising treatment modality for retina diseases for which there are significant unmet medical needs. Our efforts have resulted in the expansion of our research and development pipeline, including in 2018 and 2019, the addition of several gene therapy product candidates and collaborative sponsored research programs as well as our HtrA1 inhibitor program.

In December 2019, we completed an underwritten public offering in which we sold approximately 7,750,000 shares of our common stock, which includes shares purchased pursuant to the underwriters' option to purchase additional shares of our common stock, at a public offering price of $4.00 per share. We also sold to certain investors pre-funded warrants to purchase 3,750,000 shares of our common stock at a public offering price of $3.999 per share underlying each warrant. We raised approximately $42,600,000.0 million in net proceeds from this offering.

As we continue the development of our product candidates and programs and evaluate our overall strategic priorities, we will continue to pursue selective business development and financing opportunities that advance us toward our strategic goals. We have been, and plan to continue, exploring options for the future development and potential commercialization of Zimura, including potential collaboration and out-licensing opportunities, including for indications for which we previously developed Zimura such as wet AMD and idiopathic polypoidal choroidal vasculopathy, or IPCV. In addition, we expect to continue to evaluate, on a selective and targeted basis, opportunities to potentially obtain rights to additional product candidates and technologies for retinal diseases. We could also consider business development opportunities that also offer us a financing opportunity. We will continue to pursue capital raising opportunities when they are available on terms that are favorable to us and if the opportunity advances our strategic goals.

Financial Matters

As of December 31, 2019, we had cash and cash equivalents of $125.7 million. We believe that our cash and cash equivalents will be sufficient to fund our operations and capital expenditure requirements as currently planned into the beginning of 2022. In addition, we estimate that our year-end 2020 cash and cash equivalents will range between $60 million and $70 million. These estimates are based on our current business plan, including the continuation of our current research and development programs, including the ISEE2008 trial. These estimates do not reflect any additional expenditures, including associated development costs, in the event we in-license or acquire any new product candidates or if we commence any new sponsored research programs. We have based these estimates on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

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 had 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 had 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 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, or ASC, 730, *Research and Development*, or ASC 730.

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, 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 no longer have any 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 for that period as we had received the proceeds related to the royalty purchase liability in prior periods.

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, including for any collaborations or outlicensing of rights for further development and potential commercialization of Zimura, 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. 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 that is equal 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 patient enrollment-based milestone, and in June 2016, we achieved a further $30.0 million enrollment-based milestone, for an aggregate total of $130.0 million in milestones. 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, 2019, 2018 and 2017:

	Years ended December 31,		
	2019	2018	2017
		(in thousands)	
License revenue	$ —	$ —	$ 152,912
Research and development activity revenue	—	—	56,180
API transfer revenue	—	—	754
Joint operating committee revenue	—	—	131
Total collaboration revenue	$ —	$ —	$ 209,977

Research and Development Expenses

Our research and development expenses primarily consist of costs associated with the manufacturing, development, and preclinical and clinical testing of our product candidates and costs associated with our gene therapy sponsored research programs. 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 CDMOs for the production and analysis 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 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. 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 project area or product candidate, as shown below.

The following table summarizes our research and development expenses for the years ended December 31, 2019, 2018 and 2017:

	Years ended December 31,		
	2019	2018	2017
	(in thousands)		
Zimura	$ 13,252	$ 17,109	$ 11,986
HtrA1	459	6,900	—
RHO-adRP	7,402	1,921	—
BEST1	4,572	40	—
Other gene therapy	1,384	1,968	—
Fovista	46	(358)	21,698
Personnel-related	6,771	6,088	19,413
Share-based compensation	4,260	4,967	11,114
Other	1,498	3,102	2,078
	$ 39,644	$ 41,737	$ 66,289

As we continue our ongoing clinical trials for Zimura and initiate our planned ISEE2008 trial, we expect our research and development expenses for Zimura to increase. We also expect our research and development expenses for each of IC-100, IC-200, our miniCEP290 program and our HtrA1 inhibitors program to increase. We expect our research and development expenses for our other collaborative gene therapy sponsored research programs to decrease as the sponsored research for those programs reaches completion. Our research and development expenses may also increase if we in-license or acquire any new product candidates, including from our collaborative gene therapy sponsored research programs, or if we commence any new sponsored research programs.

Our costs may exceed our expectations if we experience any unforeseen issue in our ongoing clinical trials, such as issues with patient enrollment, the retention of enrolled patients or 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 modify or 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.

Although 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 total remaining costs necessary to complete development, to complete process development and manufacturing scale-up and validation activities and to potentially seek marketing approval for any of 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, we plan to begin the ISEE2008 trial, which is a single Phase 3 clinical trial evaluating Zimura for GA, with the expectation that data collected from this trial, if positive, together with data from our OPH2003 trial, will be sufficient to seek marketing

approval for this indication in the United States and the European Union. We may subsequently decide to, or be required by regulatory authorities to, enroll additional patients in the ISEE2008 trial beyond our current expectations or conduct additional clinical trials for Zimura in GA in order to seek or maintain regulatory approval or qualify for reimbursement approval. As a result of any of the above, we could be required to expend significant additional financial resources and time on the completion of clinical development of Zimura in GA.

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 related to our academic research collaborators, CROs, CDMOs and other vendors in connection with research and development and manufacturing activities.

We base our expenses related to academic research collaborators, CROs and CDMOs 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 are developing 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, including for any collaborations or outlicensing of rights for further development and potential commercialization of Zimura, 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 Financial Account Standards Board, or FASB, ASC, *Revenue from Contracts with Customers (Topic 606)*, or ASC 606.

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 only when the performance-based milestone is deemed probable of achievement. If performance-based milestones are later determined not to be probable of achievement, then all previously recorded stock-based compensation expense associated with such options will be reversed during the period in which we make this determination. Calculating the fair value of share-based awards requires us to make highly subjective assumptions.

Prior to January 1, 2019, share-based compensation awarded to non-employees was subject to revaluation over the vesting term of each award. Subsequent to the adoption of ASU 2018-07, *Improvements to Non-Employee Share-Based Payment Accounting*, the value of non-employee share-based compensation is measured on the date of grant, similar to share-based compensation granted to employees.

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. We calculate expected volatility based on daily historical volatility during the time period that corresponds to the expected option term. We calculate the expected term of stock option grants to employees based on an analysis of actual option exercises. 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, 2019, 2018 and 2017:

	Years ended December 31,		
	2019	2018	2017
Expected common stock price volatility	110%	85%	81%
Risk-free interest rate	1.38-2.54	2.39% - 2.95%	1.82% - 2.38%
Expected term of options (years)	4.8	6.0	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 $9.2 million, $11.1 million and $18.2 million for the years ended December 31, 2019, 2018, and 2017, respectively. As of December 31, 2019, we had $13.3 million of total unrecognized share-based compensation expense, which we expect to recognize over a weighted-average remaining vesting period of approximately 3.0 years. We expect to grant additional stock options that will result in additional share-based compensation expense for our equity awards to employees, non-employee directors and consultants.

For the years ended December 31, 2019, 2018 and 2017, we allocated share-based compensation as follows:

	Years ended December 31,		
	2019	2018	2017
		(in thousands)	
Research and development	$ 4,260	$ 4,967	$ 11,114
General and administrative	4,920	6,105	7,057
Total	$ 9,180	$ 11,072	$ 18,171

In October 2019, our board of directors adopted the 2019 Inducement Stock Incentive Plan, or the Inducement Plan, pursuant to which we may grant, subject to the terms of the Inducement Plan and the rules of The Nasdaq Global Select Market, or Nasdaq, nonstatutory stock options, restricted stock, RSUs, and other stock-based awards up to an aggregate of 1,000,000 shares of our common stock. The Inducement Plan permits us to, subject to the approval of each grant by the compensation committee of our board of directors, use the stock-based awards available under the Inducement Plan to attract key employees for the growth of our business. On October 31, 2019, we filed a Registration Statement on Form S-8 with the SEC to register under the Securities Act all shares that are issuable under the Inducement Plan. An initial award under the Inducement Plan consisting of an option to purchase 300,000 shares of our common stock and 50,000 RSUs was granted to one new employee, effective as of November 1, 2019.

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 11 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 2019, 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 Agreement and the Novartis 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, 2019.

Results of Operations

Comparison of Years Ended December 31, 2019 and 2018

	Years ended December 31,		Increase (Decrease)
	2019	2018	
	(in thousands)		
Statements of Operations Data:			
Operating expenses:			
Research and development	$ 39,644	$ 41,737	$ (2,093)
General and administrative	21,628	23,612	(1,984)
Total operating expenses	61,272	65,349	(4,077)
Loss from operations	(61,272)	(65,349)	(4,077)
Interest income	2,151	2,389	(238)
Gain on extinguishment of royalty purchase liability	—	125,000	(125,000)
Other income (expense)	151	(16)	(167)
Income (loss) before income tax benefit	(58,970)	62,024	(120,994)
Income tax benefit	(111)	(1,063)	(952)
Net income (loss)	$ (58,859)	$ 63,087	$ (121,946)

Research and Development Expenses

Our research and development expenses were $39.6 million for the year ended December 31, 2019, a decrease of $2.1 million compared to $41.7 million for the year ended December 31, 2018. The decrease in research and development expenses for the year ended December 31, 2019 was primarily due to a $6.4 million decrease in costs associated with our HtrA1 inhibitor program, a $3.9 million decrease in costs associated with our Zimura program and a $1.6 million decrease in professional services and consulting fees. The decreased costs for our HtrA1 inhibitor program related to the immediate expensing in 2018 of the in-process research and development costs of our HtrA1 inhibitor program acquired through our acquisition of Inception 4 in 2018. The decreased costs for our Zimura programs included lower costs related to a decrease in Zimura manufacturing activities and lower clinical trial costs as a result of the completion of the OPH2007 trial during the fourth quarter of 2018 and the completion of patient recruitment for the OPH2003 trial during the fourth quarter of 2018 and the associated reduction in site initiation costs. The decreased costs for our Zimura programs were partially offset by increased costs associated with the continued progress of the OPH2005 trial. The overall decrease in research and development expenses was partially offset by a $9.4 million increase in costs resulting from the expansion of our gene therapy programs.

General and Administrative Expenses

Our general and administrative expenses were $21.6 million for the year ended December 31, 2019, a decrease of $2.0 million, compared to $23.6 million for the year ended December 31, 2018. The decrease in general and administrative expenses was primarily due to a decrease of $1.6 million in personnel expenses and a decrease of $0.5 million in professional and consulting fees. The decrease in personnel expenses included a decrease of $1.2 million in share-based compensation expense as a result of a decrease in the fair value of our common stock.

Interest Income

Interest income for the year ended December 31, 2019 was $2.2 million compared to interest income of $2.4 million for the year ended December 31, 2018. The decrease in interest income earned during the year ended December 31, 2019 was the result of 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 no longer had an obligation to repay Novo the $125.0 million that it had provided us pursuant to the Novo Agreement, 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 the extinguishment of the royalty purchase liability did not impact our cash balance during that period as we had received the proceeds related to the royalty purchase liability in prior periods.

Income Tax Benefit

We recorded a benefit from income taxes of approximately $0.1 million and $1.1 million for the year ended December 31, 2019 and 2018, respectively, which primarily related to the settlement of local tax audits.

Although we had net income before income taxes during 2018, this income is primarily due to the Novo Termination Agreement. Payments received under the Novo 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.

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 income (expense)	(16)	(34)	(18)
Income (loss) before income tax benefit	62,024	109,493	(47,469)
Income tax benefit	(1,063)	(4,712)	(3,649)
Net income (loss)	$ 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 programs, including our Fovista Phase 3 clinical program and the 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 our 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 in 2018 related to in-process research and development costs for our HtrA1 inhibitor program acquired through our acquisition of Inception 4 in 2018, a $5.1 million increase in costs associated with our Zimura programs and a $3.9 million increase in costs resulting from the initiation of our gene therapy programs.
The increase in costs for our Zimura programs related to our clinical trial activities as a result of the initiation of the OPH2005 trial, the advancement of the OPH2003 trial and the completion of the OPH2007 trial. These increased clinical trial costs were partially offset by a decrease in Zimura manufacturing activities during 2018.

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 included 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. This increase in interest income was partially 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 no longer had an obligation to repay Novo the $125.0 million that it had provided us pursuant to the Novo Agreement, 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 the extinguishment of the royalty purchase liability did not impact our cash balance during that 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 and the settlement of a franchise tax audit for $1.4 million. These were 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.

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, funds we received under the Novartis Agreement, funds we received in connection with our acquisition of Inception 4 in October 2018, and our follow-on public offerings, which we closed in February 2014 and December 2019. In August 2018, we filed a universal shelf registration statement on Form S-3 with the SEC, or the Shelf Registration, 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 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.

In December 2019, we completed an underwritten public offering in which we sold approximately 7,750,000 shares of our common stock, which includes the underwriters' option to purchase additional shares of our common stock, at a public offering price of $4.00 per share, and at a price per share of $3.736 to the underwriters. We also sold to certain investors pre-funded warrants to purchase 3,750,000 shares of our common stock at a public offering price of $3.999 per share underlying each warrant, and at a purchase price of $3.735 per share underlying each warrant to the underwriters.

The net proceeds from the offering, after deducting underwriting discounts and commissions of $3.0 million and other offering expenses of $0.4 million, was approximately $42.6 million. The shares and the warrants were issued pursuant to the Shelf Registration. A prospectus supplement relating to the offering was filed with the SEC.

Cash Flows

As of December 31, 2019, we had cash and cash equivalents totaling $125.7 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, 2019, 2018 and 2017:

	Years ended December 31,		
	2019	2018	2017
		(in thousands)	
Net cash (used in) provided by:			
Operating Activities	$ (48,490)	$ (41,911)	$ (121,821)
Investing Activities	150	—	154,792
Financing Activities	42,838	6,140	71
Net change in cash and cash equivalents	$ (5,502)	$ (35,771)	$ 33,042

Cash Flows from Operating Activities

The net cash used in operating activities, which was $48.5 million and $41.9 million for the years ended December 31, 2019 and 2018, respectively, relates primarily to net cash used to fund our Zimura clinical trials and support the preclinical development activities of our gene therapy programs and our HtrA1 inhibitor program.

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

Net cash provided by investing activities for the year ended December 31, 2019 relates to the proceeds received from the sale of manufacturing and clinical equipment. We had no net cash provided by investing activities for the year ended December 31, 2018.

Cash Flows from Financing Activities

Net cash provided by financing activities for the year ended December 31, 2019 was $42.8 million and relates primarily to cash received from our December 2019 public offering of our common stock. Net cash provided by financing activities for the year ended December 31, 2018 was $6.1 million and relates primarily to cash acquired as part of the Inception 4 acquisition.

Funding Requirements

Zimura is in clinical development, our gene therapy product candidates IC-100 and IC-200 and our HtrA1 inhibitor program are each in preclinical development, and we are funding multiple ongoing collaborative gene therapy sponsored research programs. We expect our research and development expenses to increase as we pursue these programs as currently

planned and as we initiate the ISEE2008 trial. 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 Corp., or Archemix, with respect to Zimura, UFRF and Penn with respect to IC-100 and IC-200, UMass with respect to any potential product candidates from our miniCEP290 program, and the former equityholders of Inception 4 with respect to our HtrA1 inhibitor program, in each case, that impose significant milestone payment obligations on us if we achieve 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 IC-100, IC-200 and any product candidates we choose to develop from our miniCEP290 program. It is likely that any future in-licensing or acquisition agreements that we enter into for additional product candidates or technologies would include similar obligations.

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

- continue the development of Zimura in GA and STGD1;
- continue the development of IC-100 and IC-200 and pursue our collaborative gene therapy sponsored research programs;
- continue the preclinical development of our HtrA1 inhibitors program;
- 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
- hire additional clinical, manufacturing, quality control, quality assurance and scientific personnel;
- seek marketing approval for any product candidates that successfully complete clinical trials;
- in-license or acquire the rights to, and pursue the development of, other product candidates or technologies;
- maintain, expand and protect our intellectual property portfolio;
- expand our general and administrative functions to support our future growth.

As of December 31, 2019, we had cash and cash equivalents of $125.7 million. We believe that our cash and cash equivalents will be sufficient to fund our operations and capital expenditure requirements as currently planned into the beginning of 2022. In addition, we estimate that our year-end 2020 cash and cash equivalents will range between $60 million and $70 million. These estimates are based on our current business plan, including the continuation of our current research and development programs including the ISEE2008 trial. These estimates do not reflect any additional expenditures, including associated development costs, in the event we in-license or acquire any new product candidates or if we commence any new sponsored research programs. We have based these estimates on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

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. Although 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 total remaining costs necessary to complete development, to complete process development and manufacturing scale-up and validation activities and to potentially seek marketing approval for any of our product candidates.

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

- the scope, progress, costs and results of our current and planned Zimura clinical programs;
- the scope, progress, costs and results of our efforts to develop IC-100 and IC-200, including activities to establish manufacturing capabilities and preclinical testing to enable us to file INDs for these product candidates;
- the scope, progress, costs and results from our collaborative gene therapy sponsored research programs, including costs related to the in-license and future development of any promising product candidates that emerge from these programs;

- the scope, progress, costs and results of our efforts to develop our HtrA1 inhibitors program, including activities to establish manufacturing capabilities and formulation development and other preclinical development activities to enable us to file an IND for a product candidate from this program;
- the costs, progress and timing of process development, manufacturing scale-up and validation activities, analytical method development and stability studies associated with our product candidates;
- our ability to establish collaborations on favorable terms, if at all, if we choose to do so, including any collaboration for the further development and potential commercialization of Zimura;
- the extent to which we in-license or acquire rights to, and undertake research or development of, additional product candidates or technologies;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending intellectual property-related claims;
- the costs, timing and outcome of regulatory filings and reviews of our product candidates;
- scope, timing 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 and any required reimbursement approvals, 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 may require additional funding beyond what we currently expect due to unforeseen or other reasons. Our costs may exceed our expectations if we experience any unforeseen issue in our ongoing clinical trials, such as issues with patient enrollment, the retention of enrolled patients or 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 modify or 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. For example, we plan to begin the ISEE2008 trial, a single Phase 3 clinical trial evaluating Zimura for GA, with the expectation that data collected from this trial, if positive, together with data from our OPH2003 trial, will be sufficient to seek marketing approval for this indication in the United States and the European Union. We may subsequently decide to, or be required by regulatory authorities to, enroll additional patients in the ISEE2008 trial beyond our current expectations or conduct additional clinical trials for Zimura in GA in order to seek or maintain regulatory approval or qualify for reimbursement approval. As a result of any of the above, 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.

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 business, 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. Although we were able to raise approximately $42.6 million in net proceeds through our December 2019 public offering, we may not be able to successfully raise additional capital in the future. The size of our company and our status as a company listed on 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 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 issue such shares at a premium, which investors may be unwilling to accept, or 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.

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 have issued, and may in the future issue additional, equity securities as consideration for 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 be required 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. This amount does not include the milestone payment obligation of $1.0 million triggered by the positive, initial top-line data from the OPH2003 trial, which is included as a payable on our Consolidated Balance Sheet as of December 31, 2019 and as an expense on our Consolidated Statement of Operations for the year ended December 31, 2019.

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 $56.5 million if we achieve specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $23.5 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, Inc., or 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 "Licensing and Other Arrangements—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 UFRF and Penn

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—License Agreement with UFRF and Penn for IC-100" 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 RHO-adRP Master SRA, with Penn. Under the RHO-adRP 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 RHO-adRP 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 RHO-adRP 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 is not fully funded by us or do not relate to the patent rights licensed under the RHO-adRP License Agreement.

The initial term of the RHO-adRP Master SRA expires on June 6, 2021, provided that in the event of a termination of the RHO-adRP Master SRA, any statements of work in effect at the time of such termination shall continue in effect, subject to the terms of the RHO-adRP Master SRA, until expiration or termination of the applicable statement of work. Either party may terminate the RHO-adRP Master SRA or a statement of work if the other party breaches any of the terms or conditions of the RHO-adRP 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 RHO-adRP 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 RHO-adRP Master SRA pursuant to which Penn is conducting preclinical studies of IC-100, 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.

BEST1 Gene Therapy Agreements with Penn and UFRF

BEST1 License Agreement

In May 2019, we paid Penn, for the benefit of Penn and UFRF, a $0.2 million upfront license issuance fee in connection with entry into the BEST1 License Agreement, which was recorded as a research and development expense, and we paid UFRF accrued patent prosecution expenses of approximately $18 thousand, which was recorded as a general and administrative expense. We have also agreed to pay Penn, for the benefit of Penn and UFRF, an annual license maintenance fee in the low double-digit thousands of dollars, which fee will be payable on an annual basis until the first commercial sale of a licensed product. In addition, we have agreed to pay Penn, for the benefit of Penn and UFRF, a one-time patent grant fee in the low triple-digit thousands of dollars, upon the issuance of a U.S. patent that claims inventions disclosed in the licensed patent rights or know-how or inventions generated under certain related sponsored research agreements with Penn or UFRF, and that is exclusively licensed to us. Furthermore, we have agreed to reimburse Penn and UFRF for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

We have further agreed to pay Penn, for the benefit of Penn and UFRF, up to an aggregate of $15.7 million if we achieve specified clinical, marketing approval and reimbursement approval milestones with respect to one licensed product, and up to an aggregate of an additional $3.1 million if we achieve these same milestones with respect to a different licensed product. In addition, we have agreed to pay Penn, for the benefit of Penn and UFRF, up to an aggregate of $48.0 million if we achieve specified commercial sales milestones with respect to one licensed product, and up to an aggregate of an additional $9.6 million if we achieve these same milestones with respect to a different licensed product.

We are also obligated to pay Penn, for the benefit of Penn and UFRF, royalties at a low single-digit percentage of net sales of licensed products. Such royalties are subject to customary deductions, credits, and 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 to patent rights or other intellectual property rights that are necessary to research, develop, manufacture and commercialize the licensed product in such country. Our obligation to pay royalties under the BEST1 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 the sale of the applicable licensed product in the country of sale;
- the expiration of regulatory exclusivity covering the applicable licensed product in the country of sale; and
- 10 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 calendar year 2032, we are also obligated to pay certain minimum royalties, not to exceed an amount in the mid tens 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 in the year the minimum royalty is paid.

If we or any of our affiliates sublicense any of the licensed patent rights to a third party, we will be obligated to pay Penn, for the benefit of Penn and UFRF, a high single-digit to a mid ten's 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 outside the scope of the BEST1 License Agreement, we will be obligated to pay Penn, for the benefit of Penn and UFRF, aggregate payments in the low double-digit millions of dollars based on certain 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 Penn, for the benefit of Penn and UFRF, a high single-digit percentage of any consideration received from such third party in connection with such sale.

For more information about the BEST1 License Agreement, please see the section entitled "Licensing and Other Arrangements—License Agreement with Penn and UFRF for IC-200" in Part I, Item 1 of this Annual Report on Form 10-K.

BEST1 Master Sponsored Research Agreement

In October 2018, we entered into a master sponsored research agreement with Penn, which we refer to as the BEST1 Master SRA. Under the BEST1 Master SRA, Penn 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 specified in a statement of work for each project.

Under the BEST1 Master SRA, Penn has granted us an exclusive first option to obtain, for no additional consideration and pursuant to the terms of the BEST1 License Agreement, an exclusive license to any patents or patent applications resulting from the sponsored research that is fully funded by us. In addition, under the BEST1 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 is not fully funded by us.

The initial term of the BEST1 Master SRA expires on October 30, 2021, provided that in the event of a termination of the BEST1 Master SRA, any statements of work in effect at the time of such termination shall continue in effect, subject to the terms of the BEST1 Master SRA, until expiration or termination of the applicable statement of work. Either party may terminate the BEST1 Master SRA or a statement of work if the other party breaches any of the terms or conditions of the BEST1 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 BEST1 Master SRA contains indemnification and dispute resolution provisions that are customary for agreements of this kind.

We and Penn have entered into a series of statements of work under the BEST1 Master SRA pursuant to which Penn is conducting preclinical studies of IC-200, as well as natural history studies of patients with *BEST1*-related IRDs. We expect to enter into additional statements of work under the BEST1 Master SRA for additional preclinical studies. The total amount of funding for the sponsored research covered by these statements of work that we have committed to date and expect to commit to is in the low single-digit millions of dollars.

miniCEP290 License Agreement with UMass

In July 2019, we issued to UMass 75,000 shares of our common stock following execution of the miniCEP290 License Agreement pursuant to an exemption from registration afforded by Section 4(a)(2) of the Securities Act. In September 2019, we paid UMass a $0.4 million upfront license fee, which was recorded as a research and development expense, and we paid UMass accrued patent prosecution expenses of approximately $18 thousand, which was recorded as a general and administrative expense.

We have also agreed to pay UMass an annual license maintenance fee in the low double-digit thousands of dollars, which fee will be payable on an annual basis until the expiration of the royalty term for the licensed products. Furthermore, we have agreed to reimburse UMass for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

We have further agreed to pay UMass up to an aggregate of $14.75 million in cash and issue up to 75,000 shares of our common stock if we achieve specified clinical and regulatory milestones with respect to a licensed product. In addition, we have agreed to pay UMass up to an aggregate of $48.0 million if we achieve specified commercial sales milestones with respect to a licensed product.

We are also obligated to pay UMass royalties at a low single-digit percentage of net sales of licensed products. Our obligation to pay royalties under the miniCEP290 License Agreement will continue on a licensed product-by-licensed product and country-by-country basis until the later of: (a) the expiration of the last-to-expire licensed patent rights covering the sale of the applicable licensed product in the country of sale, or (b) 10 years from the first commercial sale of the applicable licensed product in the country of sale. Beginning with the calendar year following receipt of marketing approval for a licensed product, we are also obligated to pay certain minimum royalties, not to exceed an amount in the mid-double-digit 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 in the year the minimum royalty is paid.

If we or any of our affiliates sublicenses any of the licensed patent rights or know-how to a third party, we will be obligated to pay UMass a high single-digit to a mid-tens percentage of the consideration received in exchange for such sublicense, with the applicable percentage based upon the stage of development of the licensed products at the time we or the applicable affiliate enters into the sublicense.

If we receive a rare pediatric disease priority review voucher, or a 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 outside the scope of the miniCEP290 License Agreement, we will be obligated to pay UMass a low-tens percentage of the fair market value of the priority review voucher at the time of approval of such product candidate and a low-twenties percentage of the fair market value of the priority review voucher at the time of achievement of a specified commercial sales milestone for such other product candidate. In addition, if we sell such a priority review voucher to a third party, we will be obligated to pay UMass a low-thirties percentage of any consideration received from such third party in connection with such sale.

For more information about the minicCEP290 License Agreement, please see the section entitled "Licensing and Other Arrangements—License Agreement with UMass for miniCEP290 Program" in Part I, Item 1 of this Annual Report on Form 10-K.

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, 2019:

	Payments Due by Period				
	Total	Less than 1 year	1 - 3 years	3 - 5 years	More than 5 years
	(in thousands)				
Sponsored Research (1)	$ 2,357	$ 2,347	$ 10	$ —	$ —
Purchase Obligations (2)	5,623	5,603	20	—	—
Operating Leases (3)	677	557	115	5	—
Total (4)	$ 8,657	$ 8,507	$ 145	$ 5	$ —

(1) This item includes our contracted obligations under our sponsored research agreements.

(2) This item includes our contractual commitments under certain of our manufacturing and supply agreements.

(3) This item includes our continuing rent obligations, including for office space in New York, New York, the term for which is scheduled to expire at the end of June 2020.

(4) 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; or
- contracts that are entered into in the ordinary course of business that are not material in the aggregate in any period presented above.

In addition to the amounts set forth in the table above, we may be required, under the agreements under which we acquired rights to Zimura, IC-100, IC-200, our miniCEP290 program and our HtrA1 program, to make milestone payments and/or pay royalties. These payments are described in further detail in the descriptions of the applicable agreements set forth in this section.

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 2019 annual meeting of stockholders, as filed with the SEC on April 18, 2019.

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 CDMOs 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/or 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 $125.7 million as of December 31, 2019, 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 and CDMOs 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, 2019, 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-3 through F-36 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, 2019. 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, 2019, 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, 2019. 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, 2019, our internal control over financial reporting was effective.

The effectiveness of the Company's internal control over financial reporting as of December 31, 2019, 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, 2019 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 IVERIC bio, Inc.

Opinion on Internal Control over Financial Reporting

We have audited IVERIC bio, Inc.'s internal control over financial reporting as of December 31, 2019, 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, IVERIC bio, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, 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, 2019 and 2018, and the consolidated statements of operations, comprehensive income (loss), stockholders' equity and cash flows for each of the three years in the period ended December 31, 2019 and the related notes and our report dated February 27, 2020 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 27, 2020

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 2020 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Delinquent Section 16(a) Reports

The information required by this item will be set forth in our Proxy Statement for the 2020 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, or the Code of 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. In December 2019, we amended our Code of Ethics to better align the Code of Ethics with our stage of development, including, among other things, updates relating to compliance with laws, rules and regulations applicable to pharmaceutical development, interactions with healthcare providers, data privacy and international trade regulations. A copy of our Code of 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 Nasdaq concerning any amendment to, or waiver of, our Code of Ethics.

Director Nominees

The information required by this item will be set forth in our Proxy Statement for the 2020 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 2020 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 Select Market.

Item 11. Executive Compensation

The information required by this item will be set forth in our Proxy Statement for the 2020 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 2020 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 2020 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 2020 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:

(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		Certificate of Amendment to Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K filed on April 16, 2019)
3.3		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		Description of Registered Securities of the Registrant
4.2		Specimen Stock Certificate evidencing the shares of common stock
4.3		Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.1 of the Registrant's Current Report on Form 8-K filed on December 10, 2019)
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		2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 99.1 of the Registrant's Registration Statement on Form S-8 (File No. 333-234404) filed with the Securities and Exchange Commission on October 31, 2019)
10.11		Form of Restricted Stock Unit Agreement under the 2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 99.2 of the Registrant's Registration Statement on Form S-8 (File No. 333-234404) filed with the Securities and Exchange Commission on October 31, 2019)
10.12		Form of Nonstatutory Stock Option Agreement under the 2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 99.3 of the Registrant's Registration Statement on Form S-8 (File No. 333-234404) filed with the Securities and Exchange Commission on October 31, 2019)
10.13		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 and Fourth Amendment of Lease, dated as of December 22, 2014 (incorporated by reference to Exhibit 10.8 of the Registrant's Annual Report on Form 10-K filed on March 2, 2015)
10.14		Fifth Amendment of Lease, dated as of October 1, 2017, between the Registrant and One Penn Plaza LLC (incorporated by reference to Exhibit 10.11 of the Registrant's Annual Report on Form 10-K filed on March 5, 2018)
10.15		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)
10.16	†	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))
10.17	†	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)
10.18	†	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)
10.19		Amendment No. 1 to Master Sponsored Research Agreement by and between The Trustees of the University of Pennsylvania and the Registrant dated October 1, 2019 (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on November 12, 2019)
10.20	^	Exclusive License Agreement with Know-How by and among The Trustees of the University of Pennsylvania, The University of Florida Research Foundation, Incorporated, and the Registrant dated April 10, 2019 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2019)
10.21	†	Master Sponsored Research Agreement by and between The Trustees of the University of Pennsylvania and the Registrant dated October 30, 2018 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2019)
10.22		Amendment No. 1 to Master Sponsored Research Agreement by and between The Trustees of the University of Pennsylvania and the Registrant dated October 1, 2019 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on November 12, 2019)
10.23	^	Exclusive License Agreement by and between The University of Massachusetts and the Registrant dated July 22, 2019 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on November 12, 2019)
10.24	†	Clinical and Commercial Services Agreement Between the Registrant and Ajinomoto Bio-Pharma, 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)
10.25		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)

10.26	+	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))
10.27	+	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)
10.28	+	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)
10.29	+	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)
10.30	+	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)
10.31	+	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)
10.32	+	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)
10.33	+	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)
10.34	+	Letter Agreement between the Registrant and David F. Carroll, dated December 11, 2019
10.35	+	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)
10.36	+	Letter Agreement between the Registrant and Keith Westby, dated December 11, 2019
10.37	+	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)
10.38		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)
10.39		Non-Employee Director Compensation Policy of the Registrant (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on August 1, 2019)
14.1		Code of Business Conduct and Ethics of the Registrant
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.

^ Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

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 27, 2020

IVERIC bio, Inc.

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 27, 2020
/s/ DAVID F. CARROLL David F. Carroll	Senior Vice President and Chief Financial Officer (principal financial and accounting officer)	February 27, 2020
/s/ AXEL BOLTE Axel Bolte	Director	February 27, 2020
/s/ ADRIENNE L. GRAVES Adrienne L. Graves, Ph.D.	Director	February 27, 2020
/s/ DAVID R. GUYER David R. Guyer, M.D.	Executive Chairman of the Board of Directors	February 27, 2020
/s/ JANE P. HENDERSON Jane P. Henderson	Director	February 27, 2020
/s/ CALVIN W. ROBERTS Calvin W. Roberts, M.D.	Director	February 27, 2020

IVERIC bio, Inc.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of IVERIC bio, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of IVERIC bio, Inc. (the Company) as of December 31, 2019 and 2018, the related consolidated statements of operations, comprehensive income (loss), stockholders' equity and cash flows for each of the three years in the period ended December 31, 2019 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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, 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, 2019, 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 27, 2020 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.

We have served as the Company's auditor since 2008.

/s/ Ernst & Young LLP

Iselin, New Jersey
February 27, 2020

IVERIC bio, Inc.

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2019	December 31, 2018
Assets		
Current assets		
Cash and cash equivalents	$ 125,699	$ 131,201
Prepaid expenses and other current assets	2,043	2,086
Income tax receivable	882	—
Total current assets	128,624	133,287
Property and equipment, net	173	335
Right-of-use assets, net	496	—
Income tax receivable, non-current	882	3,529
Other assets	12	14
Total assets	$ 130,187	$ 137,165
Liabilities and Stockholders' Equity		
Current liabilities		
Accrued research and development expenses	$ 6,860	$ 7,337
Accounts payable and accrued expenses	5,629	5,869
Lease liability, current	495	—
Total current liabilities	12,984	13,206
Total liabilities	12,984	13,206
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, 49,627,064 and 41,397,197 shares issued and outstanding at December 31, 2019 and December 31, 2018, respectively	50	41
Additional paid-in capital	597,679	545,585
Accumulated deficit	(480,526)	(421,667)
Total stockholders' equity	117,203	123,959
Total liabilities and stockholders' equity	$ 130,187	$ 137,165

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

IVERIC bio, Inc.

Consolidated Statements of Operations

(in thousands, except per share data)

	Years ended December 31,		
	2019	**2018**	**2017**
Collaboration revenue	$ —	$ —	$ 209,977
Operating expenses:			
Research and development	39,644	41,737	66,289
General and administrative	21,628	23,612	35,683
Total operating expenses	61,272	65,349	101,972
Income (loss) from operations	(61,272)	(65,349)	108,005
Interest income	2,151	2,389	1,522
Gain on extinguishment of Royalty Purchase Liability	—	125,000	—
Other income (expense)	151	(16)	(34)
Income (loss) before income tax benefit	(58,970)	62,024	109,493
Income tax benefit	(111)	(1,063)	(4,712)
Net income (loss)	$ (58,859)	$ 63,087	$ 114,205
Net income (loss) per common share:			
Basic	$ (1.39)	$ 1.70	$ 3.18
Dilutive	$ (1.39)	$ 1.70	$ 3.17
Weighted average common shares outstanding:			
Basic	42,224	37,061	35,919
Dilutive	42,224	37,088	36,007

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

IVERIC bio, Inc.

Consolidated Statements of Comprehensive Income (Loss)

(in thousands)

	Years ended December 31,		
	2019	**2018**	**2017**
Net Income (loss)	$ (58,859)	$ 63,087	$ 114,205
Other comprehensive income			
Unrealized gain on available for sale securities, net of tax	—	—	212
Other comprehensive income	—	—	212
Comprehensive income (loss)	$ (58,859)	$ 63,087	$ 114,417

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

IVERIC bio, Inc.

Consolidated Statements of Stockholders' Equity

(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, 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 and warrants	—	—	112	—	65	—	—	65
Share-based compensation	—	—	—	—	11,072	—	—	11,072
Net income					—	63,087	—	63,087
Balance at December 31, 2018	—	$ —	41,397	$ 41	$ 545,585	$ (421,667)	$ —	$ 123,959
Issuance of common stock and pre-funded warrants through underwritten offering, net of issuance costs	—	—	7,750	8	42,557	—	—	42,565
Issuance of common stock in connection with license acquisition	—	—	75	—	85	—	—	85
Issuance of common stock under employee stock compensation plans	—	—	405	1	272	—	—	273
Share-based compensation	—	—	—	—	9,180	—	—	9,180
Net income	—	—	—	—	—	(58,859)	—	(58,859)
Balance at December 31, 2019	—	$ —	49,627	$ 50	$ 597,679	$ (480,526)	$ —	$ 117,203

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

IVERIC bio, Inc.

Consolidated Statements of Cash Flows

(in thousands)

	Years ended December 31,		
	2019	**2018**	**2017**
Operating Activities			
Net income (loss)	$ (58,859)	$ 63,087	$ 114,205
Adjustments to reconcile net loss to net cash (used in) provided by operating activities			
Depreciation	162	183	2,763
Amortization of premium and discounts on investment securities	—	—	140
Non-cash charge on acquired in-process research and development	—	5,619	—
Gain on sale of property and equipment	(150)	—	—
Non-cash gain on extinguishment of royalty purchase agreement	—	(125,000)	—
Deferred income taxes	—	—	(3,366)
Share-based compensation	9,180	11,072	18,171
Stock-based consideration in connection with license acquisition	85	—	—
Changes in operating assets and liabilities:			
Income tax receivable	1,765	1,387	(1,387)
Due from Novartis Pharma AG	—	—	3,531
Prepaid expense and other assets	45	1,070	370
Accrued interest receivable	—	—	466
Accrued research and development expenses	(477)	2,353	(42,256)
Accounts payable and accrued expenses	(241)	(1,682)	(4,481)
Deferred revenue	—	—	(209,977)
Net cash used in operating activities	(48,490)	(41,911)	(121,821)
Investing Activities			
Purchase of marketable securities	—	—	(12,014)
Maturities of marketable securities	—	—	166,806
Proceeds from sale of assets	150		—
Net cash provided by investing activities	150	—	154,792
Financing Activities			
Proceeds from issuance of common stock and pre-funded warrants, net	42,565	—	—
Proceeds from issuance of common stock related to acquisition	—	6,075	—
Proceeds from employee stock plan purchases and stock option exercises	273	65	71
Net cash provided by financing activities	42,838	6,140	71
Net change in cash and cash equivalents	(5,502)	(35,771)	33,042
Cash and cash equivalents			
Beginning of period	131,201	166,972	133,930
End of period	$ 125,699	$ 131,201	$ 166,972
Supplemental disclosure of cash paid			
Income taxes received, net	$ (1,893)	$ (2,467)	$ (245)
Supplemental disclosures of non-cash information related to investing activities			
Change in unrealized gain (loss) on available for sale securities, net of tax	$ —	$ —	$ 212
Common stock issued to acquire net assets of Inception 4, Inc.	$ —	$ 11,694	$ —
Operating right-of-use assets obtained in exchange for lease obligations	$ 1,469	$ —	$ —

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

1. Business

Description of Business and Organization

IVERIC bio, Inc. (the "Company" or "IVERIC") was incorporated on January 5, 2007, in Delaware. The Company is a science-driven biopharmaceutical company focused on the discovery and development of novel treatment options for retinal diseases with significant unmet medical needs. The Company is currently developing both therapeutics for age-related retinal diseases and gene therapy product candidates for orphan inherited retinal diseases ("IRDs"). In April 2019, the Company changed its name from Ophthotech Corporation to IVERIC bio, Inc. as it continued to broaden its focus to include gene therapies.

The Company believes that both therapeutics and gene therapy serve important roles in drug development and providing potential treatment options for patients suffering from retinal diseases. Its most advanced therapeutic product candidate is Zimura® (avacincaptad pegol), a complement C5 inhibitor. In October 2019, the Company announced initial, top-line data from a randomized, controlled clinical trial ("OPH2003 trial") of Zimura in geographic atrophy ("GA") secondary to dry age-related macular degeneration ("AMD"). The top-line data confirmed that Zimura met the prespecified primary endpoint in the trial in reducing the rate of GA growth in patients with dry AMD. The reduction in the mean rate of GA growth over 12 months using the square root transformation was 0.110 mm (p-value = 0.0072) for the Zimura 2 mg group as compared to the corresponding sham control group and 0.124 mm (p-value = 0.0051) for the Zimura 4 mg group as compared to the corresponding sham control group, indicating an approximate 27% relative reduction in the mean rate of GA growth over 12 months when compared with sham for both dose groups. These data for both dose groups were statistically significant and the Company believes demonstrate a clinically relevant reduction in rate of GA growth. Based on its review of the safety data to date, Zimura was generally well tolerated over 12 months of administration in this clinical trial. Over this 12-month period, there were no investigator-reported ocular serious adverse events, no Zimura-related adverse events, no cases of Zimura-related intraocular inflammation, no cases of Zimura-related increased intraocular pressure, no cases of endophthalmitis, and no discontinuations attributed by investigators to Zimura. OPH2003 was designed to be a Phase 2b screening trial, with the potential to qualify as a pivotal trial depending on the magnitude and statistical significance of the potential benefit observed. The Company believes that the safety and efficacy results from the OPH2003 trial could potentially satisfy the U.S. Food and Drug Administration's ("FDA's") requirements as one of the two pivotal clinical trials typically required for marketing approval of a pharmaceutical product. The Company is preparing for an international, randomized, double masked, sham controlled, multi-center Phase 3 clinical trial of Zimura in this indication ("ISEE2008 trial") with the goal of beginning patient enrollment during the first quarter of 2020.

The Company currently has two gene therapy product candidates in preclinical development and several collaborative gene therapy sponsored research programs ongoing. Subject to successful completion of preclinical development and manufacturing under current good manufacturing practices, and regulatory review, the Company plans to initiate a Phase 1/2 clinical trial for IC-100, its lead gene therapy product candidate, during the fourth quarter of 2020.

The Company's therapeutics portfolio consists of Zimura and its preclinical development program of High temperature requirement A serine peptidase 1 protein ("HtrA1") inhibitors. The Company is targeting the following diseases with Zimura:

- GA, which is the advanced stage of AMD, and is characterized by marked thinning or atrophy of retinal tissue, leading to irreversible loss of vision; and
- autosomal recessive Stargardt disease ("STGD1"), which is characterized by progressive damage to the central portion of the retina (the "macula") and other retinal tissue of young adults, leading to 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 the Company completed a Phase 2a clinical trial during the fourth quarter of 2018. The Company is developing its HtrA1 inhibitor program for GA and potentially other age-related retinal diseases.

1. Business (Continued)

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;
- IRDs associated with mutations in the *BEST1* gene, including Best vitelliform macular dystrophy ("Best disease"), which is generally characterized by bilateral egg yolk-like lesions in the macula that, over time, progress to atrophy and loss of vision;
- Leber Congenital Amaurosis type 10 ("LCA10"), which is characterized by severe bilateral loss of vision at or soon after birth;
- autosomal recessive Stargardt disease; and
- IRDs associated with mutations in the *USH2A* gene, which include Usher syndrome type 2A and *USH2A*-associated nonsyndromatic autosomal recessive retinitis pigmentosa.

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 the Company 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, 2019, the Company had cash and cash equivalents of approximately $125.7 million. The Company believes that its cash and cash equivalents as of December 31, 2019 will be sufficient to fund its operations and capital expenditure requirements as currently planned for at least the next 12 months from the filing of the Company's Annual Report on Form 10-K.

2. Summary of Significant Accounting Policies (Continued)

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, the balance of 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 the drug substance 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 on a purchase order basis the proprietary polyethylene glycol reagent used to manufacture Zimura. 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 currently relies exclusively upon a single third-party contract manufacturer for IC-100, its RHO-adRP gene therapy product candidate, and IC-200, its *BEST1*-related IRDs gene therapy product candidate, and also relies on sole-source suppliers for certain starting materials used in the manufacture of such product candidates. The Company currently relies upon a single third-party contract manufacturer to conduct process development, scale-up and GMP manufacture of the lead compound for its HtrA1 inhibitors program for potential preclinical toxicology studies and clinical trials. If the Company’s third-party manufacturers or fill/finish service providers should become unavailable to the Company for any reason, including as a result of capacity constraints, different business objectives, financial difficulties or insolvency, the Company believes that there are a limited number of potential replacement manufacturers, 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 Consolidated Statements of Operations and Comprehensive Loss. 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.

2. Summary of Significant Accounting Policies (Continued)

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.

Leases

The Company has leased its office space and has entered into various other agreements in conducting its business. At inception, the Company determines whether an agreement represents a lease and at commencement evaluates each lease agreement to determine whether the lease is an operating or financing lease. Some of the Company's lease agreements have contained renewal options, tenant improvement allowances, rent holidays and rent escalation clauses, although its remaining outstanding lease for its principal offices has no further options, allowances, holidays or clauses. As described below under "Recently Adopted Accounting Pronouncements," the Company adopted the Financial Accounting Standards Board (“FASB”) Accounting Standards Update (“ASU”) 2016-02, *Leases (Topic 842)* as of January 1, 2019.

Pursuant to ASU 2016-02, all of the Company's leases outstanding on January 1, 2019 continued to be classified as operating leases. With the adoption of ASU 2016-02, the Company recorded an operating lease right-of-use asset and an operating lease liability on its Consolidated Balance Sheet. Right-of-use lease assets represent the Company's right to use the underlying asset for the lease term and the lease obligation represents the Company's commitment to make the lease payments arising from the lease. Right-of-use lease assets and obligations are recognized at the commencement date based on the present value of remaining lease payments over the lease term. As the Company’s leases do not provide an implicit discount rate, the Company has used an estimated incremental borrowing rate based on the information available at the commencement date in determining the present value of lease payments. The right-of-use lease asset includes any lease payments made prior to commencement and excludes any lease incentives. The lease term may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. Operating lease expense is recognized on a straight-line basis over the lease term, subject to any changes in the lease or expectations regarding the terms. Variable lease costs such as common area costs and property taxes are expensed as incurred. For all office lease agreements the Company combines lease and nonlease components. Leases with an initial term of 12 months or less are not recorded on the Company's Consolidated Balance Sheet.

Prior to the adoption of ASU 2016-02, when the Company's lease agreements contained renewal options, tenant improvement allowances, rent holidays and rent escalation clauses, the Company recorded a deferred rent asset or liability equal to the difference between the rent expense and the future minimum lease payments due. The lease expense related to operating leases was recognized on a straight-line basis in the Company's Consolidated Statements of Operations over the term of each lease. In cases where the lessor granted the Company leasehold improvement allowances that reduced the Company's lease expense, the Company capitalized the improvements as incurred and recognized deferred rent, which was amortized over the shorter of the lease term or the expected useful life of the improvements.

Property and Equipment

Property and equipment, which consists mainly of clinical equipment, computers, software, 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

The Company's research and development expenses primarily consist of costs associated with the manufacturing,

2. Summary of Significant Accounting Policies (Continued)

development, and preclinical and clinical testing of the Company's product candidates and costs associated with its collaborative gene therapy sponsored research programs. The Company's 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 ("CROs") and contract development and manufacturing organizations ("CMOs") and other vendors for the production and analysis 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 collaborators.

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. 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.

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 and consultants, including employee stock options, restricted stock units ("RSUs") and options 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 only when the performance-based milestone is deemed probable of achievement. If performance-based milestones are later determined not to be probable of achievement, then all previously recorded stock-based compensation expense associated with such options will be reversed during the period in which the Company makes this determination.

The Company estimates forfeitures at the time of grant and revises those estimates in subsequent periods if actual forfeitures differ from its estimates. The Company uses 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 the Company's estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised.

Prior to January 1, 2019, share-based compensation awarded to non-employees was subject to revaluation over the vesting term of each award. Subsequent to the adoption of ASU 2018-07, Improvements to Non-Employee Share-Based Payment Accounting, the value of non-employee share-based compensation is measured on the date of grant, similar to share-based compensation granted to employees.

Stock Options

The Company estimates the fair value of stock options granted to employees, non-employees and non-employee directors on the date of grant using the Black-Scholes option-pricing model. The Company's computation of stock-price

(tabular dollars and shares in thousands, except per share data)

2. Summary of Significant Accounting Policies (Continued)

volatility is based on daily historical volatility during the time period that corresponds to the expected option term. The Company's computation of expected term is determined using the expected term of stock option grants to employees based on an analysis of actual option exercises. 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.

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, 2019, 2018 and 2017:

	Years ended December 31,		
	2019	2018	2017
Expected common stock price volatility	110%	85%	81%
Risk-free interest rate	1.38-2.54	2.39% - 2.95%	1.82% - 2.38%
Expected term of options (years)	4.8	6.0	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 Company's board of directors adopted the ESPP pursuant to which the Company may sell up to an aggregate of 1,000,000 shares of its 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,		
	2019	2018	2017
Research and development	$ 4,260	$ 4,967	$ 11,114
General and administrative	4,920	6,105	7,057
Total	$ 9,180	$ 11,072	$ 18,171

Recently Adopted 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 Topic 606, Revenue from Contracts with Customers. 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 were required to apply the amendments in ASU 2016-2 for fiscal years beginning after December 15, 2018, including interim periods within those fiscal years (i.e., January 1, 2019, for a calendar year entity). Early application was permitted for all publicly-traded business entities and all nonpublicly-traded business entities upon issuance. Lessees (for capital and operating leases) and lessors (for sales-type, direct financing, and operating leases) must

2. Summary of Significant Accounting Policies (Continued)

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 does 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. On January 1, 2019 the Company adopted this guidance utilizing the simplified transition option that allows companies to initially apply the new lease standard at the adoption date and recognize a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption. The Company elected to adopt the package of practical expedients permitted in Accounting Standards Codification Topic 842, or ASC 842. Accordingly, the Company continues to account for its existing operating leases as operating leases under the new guidance, without reassessing whether the contracts contain a lease under ASC 842 or whether classification of the operating leases would be different under ASC Topic 842.

As a result of the adoption, the Company recognized, as of the beginning of the period of adoption, right-of-use assets and lease liabilities of approximately $1.5 million, which represents the present value of its remaining lease payments using a weighted average estimated incremental borrowing rate of 6%, on its Consolidated Balance Sheet. The adoption of this standard did not have a material impact on the Company's results of operations for the year ended December 31, 2019.

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 payments arrangements related to the acquisition of goods and services from both employees and nonemployees. For public companies, the amendments became effective for annual reporting periods beginning after December 15, 2018, including interim periods within those annual periods. During the three months ended March 31, 2019, the Company adopted this guidance. The adoption did not have a material impact on its financial statements for the year ended and as of December 31, 2019.

Recent Accounting Pronouncements

In June 2016, the FASB issued ASU 2016-13 "*Financial Instruments (Topic 326) Measurement of Credit Losses on Financial Instrument*" "CECL"). ASU 2016-13 requires an allowance for expected credit losses on financial assets be recognized as early as day one of the instrument. This ASU departs from the incurred loss model which means the probability threshold is removed. It considers more forward-looking information and requires the entity to estimate its credit losses as far as it can reasonably estimate. This ASU is effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. Early adoption is permitted. The Company does not expect the adoption of this new accounting guidance to have a material impact on its financial statements or 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 does not expect the adoption of this new accounting guidance to have a material impact on its financial statements or 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 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 does not expect the adoption of this new accounting guidance to have a material impact on its financial statements or 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 does not expect the adoption of this new accounting guidance to have a material impact on its financial statements or disclosures.

(tabular dollars and shares in thousands, except per share data)

3. Common Stock

Public Offering

On December 6, 2019, the Company completed an underwritten public offering in which it sold 6,250,000 shares of its common stock at a public offering price of $4.00 per share, and it sold to certain investors pre-funded warrants to purchase 3,750,000 shares of its common stock at a public offering price of $3.999 per share underlying each warrant. The offering included an option for the underwriters to purchase up to an additional 1,500,000 shares of its common stock, which was subsequently exercised in full by the underwriters. The shares of its common stock were sold to the underwriters at a purchase price of $3.736 per share and the pre-funded warrants were sold to the underwriters at a purchase price of $3.735 per share underlying each warrant. The pre-funded warrants are immediately exercisable with certain restrictions and do not expire.

The net proceeds from the offering, after deducting underwriting discounts and commissions of $3.0 million and other offering expenses of $0.4 million, was approximately $42.6 million.

The Company evaluated the pre-funded warrants for liability or equity classification in accordance with the provisions of ASC 480, *Distinguishing Liabilities from Equity*, and ASC 815-40, *Derivatives and Hedging*. Based on the provisions governing the pre-funded warrants in the applicable agreement, the Company determined that the pre-funded warrants meet the criteria required to be classified as an equity award subject to the guidance in ASC 815-10 and 815-40 and should effectively be treated as outstanding common shares in both basic and diluted EPS calculations.

miniCEP290 Program - University of Massachusetts

On July 22, 2019, the Company entered into its exclusive license agreement with the University of Massachusetts ("UMass") for rights to its miniCEP290 program (the "miniCEP290 License Agreement"). Pursuant to the terms of the miniCEP290 License Agreement, the Company issued to UMass 75,000 shares of the Company's common stock, which were valued at approximately $0.1 million. Based on and relying on certain representations made by UMass, the Company issued those shares pursuant to an exemption from registration afforded by Section 4(a)(2) of the Securities Act of 1933, as amended (the "Securities Act").

4. 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 and pre-funded warrants outstanding during the period. For the periods when there is a net loss, shares underlying stock options and RSUs have been excluded from the calculation of diluted net loss per common share because the effect of including such shares 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,		
	2019	2018	2017
Basic and diluted net income (loss) per common share calculation:			
Net income (loss)	$ (58,859)	$ 63,087	$ 114,205
Weighted average common shares outstanding - basic	42,224	37,061	35,919
Plus: net effect of dilutive stock options and unvested restricted stock units	—	27	88
Weighted average common shares outstanding - dilutive	42,224	37,088	36,007
Net income (loss) per common share - basic	$ (1.39)	$ 1.70	$ 3.18
Net income (loss) per common share - diluted	$ (1.39)	$ 1.70	$ 3.17

(tabular dollars and shares in thousands, except per share data)

4. Net Income (Loss) Per Common Share (Continued)

The following potentially dilutive securities have been excluded from the computations of diluted weighted average common shares outstanding for the periods presented, as the effect of including such shares would be anti-dilutive:

	Years ended December 31,		
	2019	2018	2017
Stock options outstanding	6,780	5,873	5,179
Restricted stock units	1,481	601	182
Total	8,261	6,474	5,361

5. 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. As of December 31, 2019 and December 31, 2018 the Company had cash and cash equivalents of approximately $125.7 million and $131.2 million, respectively. Cash and cash equivalents at December 31, 2019 and December 31, 2018 included cash of $3.2 million and $4.4 million, respectively. As of December 31, 2019 and December 31, 2018, cash and cash equivalents also included $122.5 million and $126.8 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 considers securities with original maturities of greater than 90 days at the date of purchase to be available for sale securities. The Company held no available for sale securities at December 31, 2019 or at December 31, 2018, respectively.

The Company believes that its existing cash and cash equivalents as of December 31, 2019 will be sufficient to fund its operations and capital expenditure requirements as currently planned for at least the next 12 months from the filing of the Company's Annual Report on Form 10-K. This estimate is based on the Company's current business plan, including the continuation of its current research and development programs including the ISEE2008 trial. This estimate does not reflect any additional expenditures, including associated development costs, in the event it in-licenses or acquires any new product candidates or if it commences any new sponsored research programs. The Company has based this estimate on assumptions that may prove to be wrong, and it could use its available capital resources sooner than it currently expects.

6. Fair Value Measurements

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 investment-grade 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.

(tabular dollars and shares in thousands, except per share data)

6. Fair Value Measurements (Continued)

- 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 may 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.

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 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, 2019:

	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*	$ 108,585	$ —	$ —
Investments in corporate debt securities*	$ —	$ 13,875	$ —

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	—

* 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, 2019 or December 31, 2018.

7. 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, Inc., a Delaware corporation ("Inception 4"), 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

7. Inception 4 Acquisition (Continued)

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 closing price of the Company's common stock on the acquisition date equal to $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 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 of the Inception 4 Merger, 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 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.

8. Licensing and Commercialization Agreements

Zimura License Agreement with Archemix Corp.

In September 2011, the Company entered into an amended and restated exclusive license agreement with Archemix Corp. ("Archemix") relating to anti-C5 aptamers (as amended, the "C5 License Agreement"). The C5 License Agreement superseded a July 2007 agreement between the Company and Archemix. Under the C5 License Agreement, the Company holds 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.

In connection with the C5 License Agreement, the Company paid Archemix an upfront licensing fee of $1.0 million and issued to Archemix an aggregate of 2,000,000 shares of its series A-1 preferred stock and 500,000 shares of its series B-1 preferred stock. The Company has paid Archemix an aggregate of $2.0 million in fees based on its achievement of specified clinical milestone events under the C5 License Agreement. This amount does not include a milestone payment obligation of $1.0 million triggered by the positive, initial top-line data from the OPH2003 trial, which is included in the Company's Balance Sheet as of December 31, 2019 and its Statement of Operations for the year ended December 31, 2019.

8. Licensing and Commercialization Agreements (Continued)

Under the C5 License Agreement, for each anti-C5 aptamer product that the Company may develop under the agreement, including Zimura, it is obligated to make additional payments to Archemix of up to an aggregate of $56.5 million if it achieves specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $23.5 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, it is also obligated to make additional payments to Archemix of up to an aggregate of $22.5 million if it achieves specified commercial milestones based on net product sales of all anti-C5 products licensed under the agreement. It is also obligated to pay Archemix a double-digit percentage of specified non-royalty payments it 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.

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 the Company.

Either the Company 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 the Company's exclusive license under the agreement to a non-exclusive license, if the Company challenges or assists a third party in challenging the validity or enforceability of any of the patents licensed under the agreement. The Company may terminate the agreement at any time and for any or no reason effective at the end of a specified period following its written notice of termination to Archemix.

IC-100 Agreements with the University of Florida Research Foundation and the University of Pennsylvania

In June 2018, the Company entered into an exclusive global license agreement (the "RHO-adRP License Agreement") with the University of Florida Research Foundation, Incorporated ("UFRF") and the University of Pennsylvania ("Penn" and collectively with UFRF, 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 IC-100, the Company's novel AAV gene therapy product candidate intended to treat RHO-adRP.

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 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:

- 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

8. Licensing and Commercialization Agreements (Continued)

- 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 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 marketing approval and commercial sales milestones with respect to such other product candidate. If the Company sells such priority review voucher to a third party, it 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.

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 entered into to a Master-Sponsored Research Agreement (the "RHO-adRP MSRA"), facilitated by the Penn Center for Innovation. Under the RHO-adRP MSRA, the Company and Penn are conducting preclinical studies of IC-100, as well as a natural history study of RHO-adRP patients. The total amount of funding for the sponsored research covered by statements of work under the RHO-adRP MSRA that the Company has committed to date and is expecting to commit to is in the low single-digit millions of dollars.

IC-200 Agreements with University of Pennsylvania and University of Florida Research Foundation

In April 2019, the Company entered into an exclusive global license agreement (the "BEST1 License Agreement") with Penn and UFRF. The Company entered into the BEST1 License Agreement by exercising its exclusive option rights under an option agreement that it previously entered into with Penn and UFRF in October 2018. Under the BEST1 License Agreement, Penn and UFRF granted the Company a worldwide, exclusive license under specified patent rights and specified know-how and a worldwide, non-exclusive license under other specified know-how to research, develop, manufacture and commercialize certain AAV gene therapy products, including IC-200, for the treatment of Best disease and other *BEST1*-related IRDs.

In May 2019, the Company paid Penn, for the benefit of the Licensors, a $0.2 million upfront license issuance fee, which was recorded as a research and development expense, and the Company paid UFRF accrued patent prosecution expenses of approximately $18 thousand, which was recorded as a general and administrative expense. The Company has also agreed to pay Penn, for the benefit of the Licensors, 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 have agreed to pay Penn, for the benefit of the Licensors, a one-time patent grant fee in the low triple-digit thousands of dollars, upon the issuance of a U.S. patent that claims inventions disclosed in the licensed patent rights or know-how or inventions generated under certain related sponsored research agreements with Penn or UFRF, and that is exclusively licensed to the Company. Furthermore, it has agreed to reimburse Penn and UFRF for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

The Company has further agreed to pay Penn, for the benefit of the Licensors, up to an aggregate of $15.7 million if it achieves specified clinical, marketing approval and reimbursement approval milestones with respect to one licensed product, and up to an aggregate of an additional $3.1 million if it achieves these same milestones with respect to a different licensed product. In addition, it has agreed to pay Penn, for the benefit of the Licensors, up to an aggregate of $48.0 million if it achieves

8. Licensing and Commercialization Agreements (Continued)

specified commercial sales milestones with respect to one licensed product, and up to an aggregate of an additional $9.6 million if it achieves these same milestones with respect to a different licensed product.

The Company is also obligated to pay Penn, for the benefit of the Licensors, royalties at a low single-digit percentage of net sales of licensed products. Such royalties are subject to customary deductions, credits, and 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 in such country under third-party licenses to patent rights or other intellectual property rights that are necessary to research, develop, manufacture and commercialize the licensed product in such country. Its obligation to pay royalties under the BEST1 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 the sale of the applicable licensed product in the country of sale;
- the expiration of regulatory exclusivity covering the applicable licensed product in the country of sale; and
- 10 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 calendar year 2032, the Company is also obligated to pay certain minimum royalties, not to exceed an amount in the mid tens of thousands of dollars on an annual basis, which minimum royalties are creditable against its royalty obligation with respect to net sales of licensed products due in the year the minimum royalty is paid.

If the Company or any of its affiliates sublicense any of the licensed patent rights to a third party, it will be obligated to pay Penn, for the benefit of the Licensors, a high single-digit to a mid ten's 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 it or the applicable affiliate enters into the sublicense.

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 outside the scope of the BEST1 License Agreement, it will be obligated to pay Penn, for the benefit of the 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 candidate. In addition, if it sells such a priority review voucher to a third party, it will be obligated to pay Penn, for the benefit of the Licensors, a high single-digit percentage of any consideration received from such third party in connection with such sale.

The BEST1 License Agreement, unless earlier terminated by the Company or Penn or UFRF, will expire upon the expiration of the Company's obligation to pay royalties on net sales of licensed products. Before the effectiveness of an IND for a licensed product, the Company may terminate the BEST1 License Agreement with respect to such licensed product or in its entirety, at any time for any reason upon prior written notice to Penn and UFRF. Following the effectiveness of an IND for a licensed product, it may terminate the BEST1 License Agreement with respect to such licensed product by providing Penn prior written notice and a certification that it is ceasing all use, research and development and commercialization of such licensed product, subject to certain limited exceptions. It may also terminate the BEST1 License Agreement if Penn or UFRF materially breaches the BEST1 License Agreement and does not cure such breach within a specified cure period.

Penn or UFRF may terminate the BEST1 License Agreement if the Company materially breaches the BEST1 License Agreement and does not cure such breach within a specified cure period, if it experiences a specified insolvency event, if it ceases to carry on the entirety of its business related to the licensed patent rights, if it ceases 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 the Company is actively attempting to address, or if it, any of its affiliates or any of its sublicensees challenges or assists a third party in challenging the validity, scope, patentability, and/or enforceability of the licensed patent rights. If it materially breaches certain diligence obligations under the BEST1 License Agreement with respect to only one licensed product, then Penn and UFRF may only terminate its rights and licenses under the BEST1 License Agreement for such licensed product, but not for other licensed products.

8. Licensing and Commercialization Agreements (Continued)

In addition to the exclusive license agreement, the Company and Penn also entered into a Master-Sponsored Research Agreement (the "BEST1 MSRA"), facilitated by the Penn Center for Innovation. Under the BEST1 MSRA, the Company and Penn are conducting preclinical studies of IC-200, as well as natural history studies of patients with *BEST1*-related IRDs. The Company expects to enter into additional statements of work under the BEST1 MSRA for additional preclinical studies. The total amount of funding for the sponsored research covered by statements of work under the BEST1 MSRA that the Company has committed to date and expects to commit to is in the low single-digit millions of dollars.

License Agreement with University of Massachusetts for the miniCEP290 Program

In July 2019, the Company entered into the miniCEP290 License Agreement with UMass by exercising its exclusive option rights under an option agreement and a sponsored research agreement that it previously entered into with UMass in February 2018. Under the miniCEP290 License Agreement, UMass granted it a worldwide, exclusive license under specified patent rights and specified biological materials and a non-exclusive license under specified know-how to make, have made, use, offer to sell, sell, have sold and import products for the treatment of diseases associated with mutations in the *CEP290* gene, including LCA10.

In July 2019, the Company issued to UMass 75,000 shares of its common stock following execution of the miniCEP290 License Agreement pursuant to an exemption from registration afforded by Section 4(a)(2) of the Securities Act. In September 2019, it paid UMass a $0.4 million upfront license fee, which was recorded as a research and development expense, and it paid UMass accrued patent prosecution expenses of approximately $18 thousand, which was recorded as a general and administrative expense.

The Company has also agreed to pay UMass an annual license maintenance fee in the low double-digit thousands of dollars, which will be payable on an annual basis until the expiration of the royalty term for the licensed products. Furthermore, it has agreed to reimburse UMass for the costs and expenses of patent prosecution and maintenance related to the licensed patent rights.

The Company has further agreed to pay UMass up to an aggregate of $14.75 million in cash and issue up to 75,000 shares of its common stock if it achieves specified clinical and regulatory milestones with respect to a licensed product. In addition, the Company has agreed to pay UMass up to an aggregate of $48.0 million if it achieves specified commercial sales milestones with respect to a licensed product.

The Company is also obligated to pay UMass royalties at a low single-digit percentage of net sales of licensed products. Its obligation to pay royalties under the miniCEP290 License Agreement will continue on a licensed product-by-licensed product and country-by-country basis until the later of: (a) the expiration of the last-to-expire licensed patent rights covering the sale of the applicable licensed product in the country of sale, or (b) 10 years from the first commercial sale of the applicable licensed product in the country of sale. Beginning with the calendar year following receipt of marketing approval for a licensed product, it is also obligated to pay certain minimum royalties, not to exceed an amount in the mid-double-digit thousands of dollars on an annual basis, which minimum royalties are creditable against its royalty obligation with respect to net sales of licensed products due in the year the minimum royalty is paid.

If the Company or any of its affiliates sublicenses any of the licensed patent rights or know-how to a third party, it will be obligated to pay UMass a high single-digit to a mid-tens percentage of the consideration received in exchange for such sublicense, with the applicable percentage based upon the stage of development of the licensed products at the time it or the applicable affiliate enters into the sublicense.

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 it subsequently uses such priority review voucher in connection with a different product candidate outside the scope of the miniCEP290 License Agreement, it will be obligated to pay UMass a low-tens percentage of the fair market value of the priority review voucher at the time of approval of such product candidate and a low-twenties percentage of the fair market value of the priority review voucher at the time of achievement of a specified commercial sales milestone for such other product candidate. In addition, if it sells such a priority review voucher to a third party, it will be

8. Licensing and Commercialization Agreements (Continued)

obligated to pay UMass a low-thirties percentage of any consideration received from such third party in connection with such sale.

The miniCEP290 License Agreement, unless earlier terminated by the Company or UMass, will expire upon the expiration of its obligation to pay royalties to UMass on net sales of licensed products. The Company may terminate the miniCEP290 License Agreement at any time for any reason upon prior written notice to UMass. It may also terminate the miniCEP290 License Agreement if UMass materially breaches the miniCEP290 License Agreement and does not cure such breach within a specified cure period.

UMass may terminate the miniCEP290 License Agreement if the Company materially breaches the miniCEP290 License Agreement and does not cure such breach within a specified cure period.

Prior Licensing and Commercialization Agreement with Novartis Pharma AG

Prior to 2018, the Company's revenues 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 $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

(tabular dollars and shares in thousands, except per share data)

8. Licensing and Commercialization Agreements (Continued)

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 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, 2019, 2018, and 2017:

	Years ended December 31,		
	2019	2018	2017
License revenue	$ —	$ —	$ 152,912
Research and development activity revenue	—	—	56,180
API transfer revenue	—	—	754
Joint operating committee revenue	—	—	131
Total collaboration revenue	$ —	$ —	$ 209,977

(tabular dollars and shares in thousands, except per share data)

9. 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 ("Novo" and 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 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"). The Company received the cash payments from Novo 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.

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, the Company treated its obligation to make royalty payments under the Novo Agreement as an implicit obligation to repay the funds advanced by Novo.

On December 31, 2018, the Company and Novo entered into a letter agreement (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, 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 any right or license in any such intellectual property rights or clinical study data generated by or on behalf of the Company, its affiliates, 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 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 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 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. The extinguishment of the royalty purchase liability and the related gain did not impact the Company's cash balance during that period, as the Company had received the proceeds related to the royalty purchase liability in prior periods.

10. Property and Equipment

Property and equipment as of December 31, 2019 and 2018 were as follows:

	Useful Life (Years)	December 31, 2019	December 31, 2018
Manufacturing and clinical equipment	7 - 10	$ 47	$ 412
Computer, software and other office equipment	5	933	933
		980	1,345
Accumulated depreciation		(807)	(1,010)
Property and equipment, net		$ 173	$ 335

For the years ended December 31, 2019, 2018 and 2017, depreciation expense was $0.2 million, $0.2 million and $2.8 million, respectively.

(tabular dollars and shares in thousands, except per share data)

11. Income Taxes

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.

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,		
	2019	2018	2017
Percent of pre-tax income:			
U.S. federal statutory income tax rate	21.0 %	21.0 %	35.0 %
State taxes, net of federal benefit	10.9 %	18.5 %	14.6 %
Permanent items	(1.0)%	4.0 %	4.0 %
Remeasurement of deferred tax assets	— %	— %	49.9 %
Impact of state rate changes	0.1 %	(0.2)%	(27.9)%
Research and development credit	2.8 %	(2.4)%	— %
Alternative minimum tax credit	— %	— %	(1.3)%
Change in valuation allowance	(33.6)%	(42.6)%	(78.6)%
Effective income tax rate	0.2 %	(1.7)%	(4.3)%

The components of income tax benefit are as follows:

	Years ended December 31,		
	2019	2018	2017
Current:			
Federal	$ —	$ —	$ 173
State	(111)	(1,063)	(1,356)
Deferred:			
Federal	—	—	(3,529)
State	—	—	—
Income tax benefit	$ (111)	$ (1,063)	$ (4,712)

(tabular dollars and shares in thousands, except per share data)

11. Income Taxes (Continued)

Significant components of the Company's deferred tax assets (liabilities) for 2019 and 2018 consist of the following:

	As of December 31,	
	2019	2018
Deferred tax assets (liabilities)		
License and technology payments	7,116	7,221
Share-based compensation	22,131	20,342
Accrued expenses	362	371
Right-of-use asset	(163)	—
Lease obligation	162	—
Depreciation	(18)	(28)
Federal and state net operating loss carryforwards	105,375	88,766
Research and development credits	7,353	5,933
Other	6	5
Deferred income tax assets	142,324	122,610
Valuation allowance	(142,324)	(122,610)
Net deferred tax assets	$ —	$ —

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 2019 and 2018. The Company has carried forward its federal and state tax losses due to the inability of carryback claims. Federal NOLs incurred prior to 2018 will begin to expire in 2034 if not utilized. Post 2017 Federal NOLs have an unlimited life. The state NOLs are expected to begin to expire in 2028. Due to the Company's history of losses and lack of other positive evidence to support taxable income, the Company has recorded a valuation allowance against those remaining deferred tax assets that are not expected to be realized. As of December 31, 2019, the Company has federal NOL carryforwards of approximately $369.7 million.

For the year ended December 31, 2019 and 2018, the Company recorded a benefit from income taxes of $0.1 million and $1.1 million, respectively, due primarily to the settlements of a local tax audits. For the year ended December 31, 2017, the Company recorded a benefit from income taxes 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 2019, the Company received $1.8 million related to the refund of the afore-mentioned AMT credits and recorded a tax receivable of $1.8 million to reflect the refund of AMT credits it expects to receive over the next three years.

The Company generated net income before income taxes for the years ended December 31, 2018 and 2017. This income was 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, 2019.

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.

(tabular dollars and shares in thousands, except per share data)

11. 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, 2019, the Company reduced certain deferred tax assets by $19.7 million and increased 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 $4.8 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	$	13,983
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		18
Gross amount of decreases in unrecognized tax benefits during the period - other		(1,579)
Decreases due to settlement with tax authorities during the period		(195)
Reduction of unrecognized tax benefits due to expiration of the state of limitations during the period.		—
Closing Balance	$	12,227

As the Company is currently under audit 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 $4.8 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.

12. Operating Leases

The Company leases office space located in New York, New York and Princeton, New Jersey under non-cancelable operating lease arrangements. The lease for the Company's New York office expires at the end of June 2020, and the sublease for the Company's Princeton office expires in March 2020. As of January 1, 2019, the Company recognized right-of-use assets and lease liabilities of approximately $1.5 million, which represents the present value of its remaining lease payments using a weighted average estimated incremental borrowing rate of 6%.

For the years ended December 31, 2019, 2018 and 2017, lease and rent expense was $1.0 million, $0.8 million and $3.6 million, respectively. Cash paid from operating cash flows for amounts included in the measurement of lease liabilities was $1.0 million year ended December 31, 2019. At December 31, 2019, the Company's operating leases had a weighted average remaining lease term of 0.5 years.

The following presents the maturity of the Company's operating lease liabilities as of December 31, 2019:

	December 31, 2019	
2020	$	504
Total remaining obligation.	$	504
Less imputed interest	$	(9)
Present value of lease liabilities	$	495

12. Operating Leases (Continued)

During December 2019, the Company entered into a lease for office space located in Cranbury, New Jersey. The Company has recognized a right-of-use asset and lease liability of approximately $0.2 million when the lease commenced in February 2020. The term of the lease for the Company's Cranbury office expires at the end of February 2023.

13. Commitments and Contingencies

Zimura - Archemix Corp.

The Company is party to an agreement with Archemix Corp., or 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 (the "C5 License Agreement"). In October 2019, following its announcement of positive, initial top-line data from the OPH2003 trial, the Company became obligated under the C5 License Agreement to pay Archemix a clinical milestone of $1.0 million, which is recorded as a payable in the Company's Consolidated Balance Sheet as of December 31, 2019 and as an expense in the Consolidated Statement of Operations for the year ended December 31, 2019. In addition, for each anti-C5 aptamer product that the Company may develop under the agreement, including Zimura, the Company is obligated to make additional payments to Archemix of up to an aggregate of $56.5 million if the Company achieves specified development, clinical and regulatory milestones, with $30.5 million of such payments relating to a first indication, $23.5 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 licensed products. 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.

IC-100 - University of Florida Research Foundation and the University of Pennsylvania

Under its exclusive license agreement with UFRF and Penn for rights to IC-100, the Company is obligated to make payments to UFRF, for the benefit of the 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, for the benefit of the Licensors, a low single-digit percentage of net sales of licensed products. The Company is also obligated to pay UFRF, for the benefit of the 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, for the benefit of the 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 candidate. In addition, if the Company sells such a priority review voucher to a third party, the Company will be obligated to pay UFRF, for the benefit of the Licensors, a low double-digit percentage of any consideration received from such third party in connection with such sale.

IC-200 - University of Pennsylvania and the University of Florida Research Foundation

Under its exclusive license agreement with Penn and UFRF for rights to IC-200, the Company is obligated to make payments to Penn, for the benefit of the Licensors, of up to an aggregate of $15.7 million if the Company achieves specified clinical, marketing approval and reimbursement approval milestones with respect to one licensed product and up to an aggregate of an additional $3.1 million if the Company achieves these same milestones with respect to a different licensed product. In addition, the Company is obligated to make payments to Penn, for the benefit of the Licensors, of up to an aggregate of $48.0 million if the Company achieves specified commercial sales milestones with respect to one licensed product and up to an aggregate of an additional $9.6 million if the Company achieves these same milestones with respect to a different licensed product. The Company is also obligated to pay Penn, for the benefit of the Licensors, a low single-digit percentage of net sales of licensed products. The Company is also obligated to pay Penn, for the benefit of the Licensors, a high single-digit to a mid-ten's percentage of specified non-royalty payments the Company may receive from any third-party sublicensee of the licensed

13. Commitments and Contingencies (Continued)

patent rights, with the applicable percentage based upon the stage of development of the sublicensed product at the time the Company enters into the sublicense. 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 outside the scope of the agreement, the Company will be obligated to pay Penn, for the benefit of the 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 candidate. In addition, if the Company sells such a priority review voucher to a third party, the Company will be obligated to pay Penn, for the benefit of the Licensors, a high single-digit percentage of any consideration received from such third party in connection with such sale.

miniCEP290 Program - University of Massachusetts

Under the miniCEP290 License Agreement, the Company is obligated to pay UMass up to an aggregate of $14.75 million in cash and issue up to 75,000 shares of common stock of the Company if the Company achieves specified clinical and regulatory milestones with respect to a licensed product. In addition, the Company is obligated to pay UMass up to an aggregate of $48.0 million if the Company achieves specified commercial sales milestones with respect to a licensed product. The Company is also obligated to pay UMass royalties at a low single-digit percentage of net sales of licensed products. If the Company or any of its affiliates sublicenses any of the licensed patent rights or know-how to a third party, the Company will be obligated to pay UMass a high single-digit to a mid-tens percentage of the consideration received in exchange for such sublicense, with the applicable percentage based upon the stage of development of the licensed products at the time the Company or the applicable affiliate enters into the sublicense. If the Company receives a 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 outside the scope of the agreement, the Company will be obligated to pay UMass a low-tens percentage of the fair market value of the priority review voucher at the time of approval of such product candidate and a low-twenties percentage of the fair market value of the priority review voucher at the time of achievement of a specified commercial sales milestone for such product candidate. In addition, if the Company sells such a priority review voucher to a third party, the Company will be obligated to pay UMass a low-thirties percentage of any consideration received from such third party in connection with such sale.

HtrA1 Inhibitors - 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 of the Inception 4 Merger, 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

13. Commitments and Contingencies (Continued)

and CDMOs 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 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. IVERIC bio, Inc., 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. IVERIC bio, Inc., 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. On September 18, 2019, the court issued an order dismissing some, but not all, of the allegations in the CAC. On November 18, 2019, the Company and the individual defendants filed an answer to the complaint. This case is currently in the discovery phase.

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. The court approved the settlement at a hearing on March 12, 2019. As part of the settlement, in April 2019 the Company paid $0.3 million in fees and costs to plaintiff's counsel. As contemplated by the settlement, the Company's board of directors adopted certain compensation-related governance reforms, including a non-employee director compensation policy, which its stockholders approved on May 15, 2019 at its 2019 annual meeting.

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. On September 19, 2019, the court denied its motion to dismiss this complaint. This matter was subsequently referred to a special litigation committee of the Company's board of directors. On February 18, 2020, the Company filed an answer to the complaint.

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

13. Commitments and Contingencies (Continued)

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. These shareholder demands have been referred to a demand review committee of the Company's board of directors.

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.

14. Stock-Based Compensation 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 10,539,000 additional shares to the 2013 Plan, including for 2020, an increase of approximately 1,985,000 shares, or 4% of the total number of shares of the Company's common stock outstanding as of January 1, 2020. As of December 31, 2019, the Company had approximately 732,000 shares available for grant under the 2013 Plan.

In October 2019, the Company's board of directors adopted the 2019 Inducement Stock Incentive Plan (the "2019 Inducement Plan") to reserve 1,000,000 shares of its common stock to be used exclusively for grants of awards to individuals that were not previously employees or directors of the Company as a material inducement to such individuals' entry into employment with the Company within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules. The terms and conditions of the 2019 Inducement Plan are substantially similar to those of the 2013 Plan. As of December 31, 2019, the Company had approximately 650,000 shares available for grant under the 2019 Inducement Plan.

14. Stock-Based Compensation and Compensation Plans (Continued)

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.

A summary of the stock option activity, weighted average exercise prices, options outstanding and exercisable as of December 31, 2019, 2018 and 2017 is as follows (in thousands except weighted average exercise price):

	Years ended December 31,					
	2019		2018		2017	
	Common Stock Options	Weighted Average Exercise Price	Common Stock Options	Weighted Average Exercise Price	Common Stock Options	Weighted Average Exercise Price
Outstanding, December 31, 2018	5,903	$ 13.72	5,284	$ 19.58	3,359	$ 39.92
Granted	1,610	$ 4.26	1,293	$ 1.67	3,024	$ 3.50
Exercised	(80)	$ 2.66	—	$ —	(20)	$ 1.64
Expired or forfeited	(653)	$ 21.16	(674)	$ 36.54	(1,079)	$ 38.17
Outstanding, December 31, 2019	6,780	$ 10.89	5,903	$ 13.72	5,284	$ 19.58

	Years ended December 31,		
	2019	2018	2017
Options exercisable at December 31, 2019	3,317	2,709	1,954
Weighted average grant date fair value (per share) of options granted during the period	$ 3.37	$ 1.20	$ 2.45

As of December 31, 2019, there were approximately 6,468,000 options outstanding, net of estimated forfeitures, that had vested or are expected to vest. The weighted-average exercise price of these options was $11.24 per option; the weighted-average remaining contractual life of these options was 7.7 years; and the aggregate intrinsic value of these options was approximately $10.6 million. A summary of the stock options outstanding and exercisable as of December 31, 2019 is as follows (in thousands except exercise prices and weighted average exercise price):

	December 31, 2019				
		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
$1.13-$2.79	1,350	8.8	$ 1.59	433	$ 1.76
$2.80-$2.96	1,725	7.9	$ 2.93	876	$ 2.93
$2.97-$4.87	1,444	8.1	$ 4.18	648	$ 4.48
$4.88-$31.09	1,090	8.7	$ 7.13	216	$ 14.89
$31.10-$73.22	1,171	5.1	$ 45.14	1,144	$ 45.01
	6,780	7.8	$ 10.89	3,317	$ 18.38
Aggregate Intrinsic Value	$ 28,475			$ 10,557	

14. Stock-Based Compensation and Compensation Plans (Continued)

Cash proceeds from, and the aggregate intrinsic value of, stock options exercised during the years ended December 31, 2019, 2018 and 2017, respectively, were as follows:

	Years ended December 31,		
	2019	2018	2017
Cash proceeds from options exercised	$ 192	$ —	$ 33
Aggregate intrinsic value of options exercised	$ 135	$ —	$ 43

In connection with stock option awards granted to employees, the Company recognized approximately $5.9 million, $7.6 million and $13.1 million in share-based compensation expense during the years ended December 31, 2019, 2018 and 2017, respectively, net of expected forfeitures. As of December 31, 2019, there were approximately $8.0 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 3.1 years.

In connection with stock option awards granted to consultants, the Company recognized approximately $0.3 million, $0.2 million and $0.3 million in share-based compensation expense during the years ended December 31, 2019, 2018 and 2017, respectively, net of expected forfeitures. As of December 31, 2019, 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 3.6 years.

The following table presents a summary of the Company's outstanding RSU awards granted as of December 31, 2019 (in thousands except weighted average grant-date fair value):

	Restricted Stock Units	Weighted Average Grant-Date Fair Value
Outstanding, December 31, 2018	679	$ 15.61
Awarded	1,090	$ 4.57
Vested	(255)	$ 13.94
Forfeited	(33)	$ 16.35
Outstanding, December 31, 2019	1,481	$ 7.79

As of December 31, 2019, there were approximately 1,287,000 RSUs outstanding, net of estimated forfeitures, that are expected to vest. The weighted-average fair value of these RSUs was $5.39 per share; and the aggregate intrinsic value of these RSUs was approximately $11.0 million.

In connection with RSUs granted to employees, the Company recognized approximately $3.0 million, $3.3 million and $4.4 million in share-based compensation expense during the years ended December 31, 2019, 2018 and 2017, respectively, net of expected forfeitures. As of December 31, 2019, there was approximately $5.0 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 2.7 years. The total fair value of the RSUs that vested during the year ended December 31, 2019 was $3.6 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, 2019, net of expected forfeitures. In connection with RSUs granted to consultants, the Company recognized approximately $0.1 million in share-based compensation expense during the year ended December 31, 2018. As of December 31, 2019, 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 3.4 years.

In connection with the ESPP made available to employees, the Company recognized approximately $0.1 million and a de minimis amount of share-based compensation expense during the years ended December 31, 2019 and December 31, 2018,

(tabular dollars and shares in thousands, except per share data)

14. Stock-Based Compensation and Compensation Plans (Continued)

respectively, net of expected forfeitures. As of December 31, 2019, 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 70,466 shares of common stock issued under the ESPP during the year ended December 31, 2019. Cash proceeds from ESPP purchases were approximately $81 thousand during the year ended December 31, 2019. There were 31,413 shares of common stock issued under the ESPP during the year ended December 31, 2018. As of December 31, 2019, 881,763 shares were available for future purchases under the ESPP.

15. 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, $0.2 million and $0.7 million during the years ended December 31, 2019, 2018 and 2017, respectively.

16. Selected Quarterly Financial Information (unaudited)

The following is a summary of the quarterly results of operations for the years ended December 31, 2019 and 2018:

	2019			
	March 31	June 30	September 30	December 31
Research and development expenses	7,685	10,009	10,383	11,567
General and administrative expenses	5,481	5,198	4,674	6,275
Loss from operations	(13,166)	(15,207)	(15,057)	(17,842)
Net income (loss) attributable to common stockholders	$ (12,501)	$ (14,443)	$ (14,437)	$ (17,478)
Basic earnings (loss) per common share	$ (0.30)	$ (0.35)	$ (0.35)	$ (0.39)
Diluted earnings (loss) per common share	$ (0.30)	$ (0.35)	$ (0.35)	$ (0.39)

	2018			
	March 31	June 30	September 30	December 31
Research and development expenses	7,686	8,516	9,407	16,128
General and administrative expenses	5,645	6,332	5,968	5,667
Income (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