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, 2022

Or

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

For the transition period from to

Commission file number 001-36080

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.)
8 Sylvan Way	
Parsippany NJ	**07054**
(Address of principal executive offices)	(Zip Code)

(609) 474-6455

(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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒ Yes ☐ No

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

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

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

As of June 30, 2022, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $1,093.4 million, based on the closing price of the registrant's common stock on June 30, 2022.

The number of shares outstanding of the registrant's class of common stock, as of February 27, 2023: 137,122,338

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report incorporates by reference information from the definitive Proxy Statement for the registrant's 2023 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, 2022.

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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, including our goal to deliver treatment options for various stages of age-related macular degeneration (AMD);
- our expectations regarding the impact of results from GATHER1, our completed Phase 3 clinical trial evaluating avacincaptad pegol (ACP) for the treatment of Geographic Atrophy (GA) secondary to AMD, and from GATHER2, our ongoing Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD, on our business and regulatory strategy, including, the timing and response to our new drug application (NDA) submitted to the U.S. Food and Drug Administration (FDA), our plans to submit marketing authorization applications to the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), and our expectations for using ACP for the treatment of intermediate AMD;
- the timing, costs, conduct and outcome of GATHER2, including expectations regarding patient retention and the safety profile of ACP, including from our open-label extension study for patients who completed the GATHER2 trial, and expectations regarding the potential for ACP to receive regulatory approval for the treatment of GA based on the clinical trial results we have received to date;
- our plans and strategy for the potential commercialization of ACP, including hiring of medical affairs and commercialization personnel, building a commercialization infrastructure, including sales, marketing and distribution capabilities, and our expectations regarding the market dynamics for treatments for GA and other commercial matters;
- our ability to establish and maintain capabilities and capacity for the manufacture of ACP and our other product candidates, including scale up and validation of the manufacturing process for ACP drug substance and drug product, and securing the supply of the polyethylene glycol (PEG) starting material and other materials for our expected manufacturing needs and securing the supply of ACP drug substance, drug product and finished goods for our expected needs;
- our plans for evaluating, obtaining rights to, developing and potentially commercializing new formulations of ACP with the silica-based sustained release technology we in-licensed from DelSiTech Ltd. (DelSiTech) and other sustained release delivery technologies for ACP;
- the timing, costs, conduct and outcome of STAR, our ongoing Phase 2b screening trial evaluating ACP for the treatment of autosomal recessive Stargardt disease, including expectations regarding the recruitment of additional patients for this trial;
- our plans and ability to consummate business development transactions, including potential collaboration opportunities for further development and potential commercialization of ACP outside the United States; and in-licenses or other opportunities to acquire rights to additional product candidates or technologies to treat retinal diseases, including additional sustained release delivery technologies for ACP;
- our estimates regarding expenses, future revenues and debt service obligations, the sufficiency of our cash resources and our capital requirements and need for, and ability to obtain, additional financing;
- our plans to raise additional capital, including through equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements, royalty agreements and marketing and distribution arrangements;

- the timing, costs, conduct and outcome of our ongoing 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;

- the timing of and our ability to submit investigational new drug applications for, and to submit new drug applications or marketing authorization applications for and to obtain marketing approval of our product candidates, and the ability of our product candidates to meet existing or future regulatory standards;

- the potential advantages of our product candidates and other technologies that we are pursuing, including our hypotheses regarding complement factor C5 inhibition and HtrA1 inhibition as potentially relevant mechanisms of action to treat GA and other stages of AMD, 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;

- our estimates regarding the potential market opportunity for our product candidates, including our ability to obtain coverage and reimbursement for those product candidates, if approved;

- 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;

- the actual and expected effects of the COVID-19 pandemic, other macro-economic events and related response measures on our business and operations, including the timing, costs, conduct and outcome of our research and development programs, our supply chain, the work of our third-party vendors and collaborators, the work and well-being of our employees, and our financial position;

- our personnel and human capital resources;

- 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 under the section "Summary of Principal Risk Factors" below and the risk factors detailed further in Item 1A, "Risk Factors" of Part I of this report and in our Securities and Exchange Commission reports filed after this report, 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.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information.

Summary of Principal Risk Factors

The following is a summary of the principal factors that make an investment in our company speculative or risky. This summary does not address all of the risks and uncertainties that we face. Additional risk and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Additional discussion of the risks summarized in this summary, and other risks that we face, can be found in Item 1A. Risk Factors section of this Annual Report on Form 10-K, and should be carefully considered, together with other information in this Annual Report on Form 10-K and our other filings with the Securities Exchange Commission, before making an investment decision regarding our common stock. The forward-looking statements discussed above 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.

1. The value of your investment is highly dependent on the success and potential commercialization of ACP. We are working to transition to being a company capable of commercializing a pharmaceutical product, if approved, and may not be successful in this transition.

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

3. We may need additional financing in order to commence, if approved, and continue commercializing ACP, or continue developing our other product candidates. Securing financing may be challenging and/or dilutive to our shareholders, and if we are unable to secure financing when needed, we may need to curtail our development programs or planned commercialization activities.

4. The covenants in our Loan and Security Agreement with Hercules Capital, Inc. and Silicon Valley Bank may limit and restrict from us from pursuing certain operating activities. If we are in default under that agreement, we may need to repay all existing indebtedness under that term loan facility.

5. We need to satisfy numerous regulatory requirements in order to secure marketing approval and reimbursement approval, if applicable, for ACP and other product candidates. These requirements differ across jurisdictions. Failure to satisfy and maintain those requirements can preclude us from commercializing our products.

6. Regulatory authorities, including the FDA and EMA, may disagree with our analyses or conclusions from our clinical trials of ACP in GA secondary to AMD. Since receipt of the 12-month results from GATHER1, we have not had any formal interactions with the EMA regarding our planned regulatory pathway for ACP in GA and the EMA and other regulatory authorities may disagree with the requirements of the FDA. We may need to conduct additional clinical trials or nonclinical studies for ACP in order to obtain marketing approval or reimbursement approval.

7. Manufacturing our product candidates is technically complex, expensive and time consuming. We may face issues with scaling up and validating the manufacturing process for ACP. We may not be able to secure adequate supply of PEG starting material, ACP drug substance, ACP drug product or ACP finished goods for our future needs, including potential commercial launch. Issues with manufacturing can derail the further development or commercialization of our product candidates.

8. To commercialize any of our product candidates, if approved, we will need to set up a sales and marketing infrastructure. We are continuing to hire commercialization personnel and will need to continue building our commercial infrastructure. The success of our commercialization efforts will depend in part on the degree of acceptance of our product candidates by patients, the medical community and payors.

9. We face substantial competition from large pharmaceutical companies, smaller biotech companies and others.

10. Drug development is inherently risky with numerous scientific, technical, regulatory and other challenges. A promising drug candidate can fail at any time and for any number of reasons.

11. We are pursuing the development of our product candidates using novel mechanisms of action targeting indications for which there are few or no approved products. These include, for example, complement inhibition and inhibition of High temperature requirement A serine peptidase 1 protein for GA, and complement inhibition for intermediate AMD and autosomal recessive Stargardt disease. These approaches carry numerous scientific, regulatory and other risks.

12. The 12-month results of GATHER2 may not be replicated by the 24-month results from the trial, which may not replicate the results of the GATHER1 trial. We may discover safety issues with our product candidates due to known and currently unknown factors, which could hamper their further development or commercialization.

13. We may not be successful in developing a formulation of ACP with the sustained release delivery technology we in-licensed from DelSiTech or obtaining rights to and developing other sustained release delivery technologies for ACP.

14. We do not have any internal manufacturing facilities and rely heavily on our third-party contract manufacturers. They may have different business priorities than we do and may fail to meet our expectations or follow regulatory requirements, including current good manufacturing practices and data integrity requirements. We may need to engage alternative manufacturers or suppliers sooner than we currently expect.

15. We plan to rely on third-party distribution and other commercial services vendors to assist us with the commercialization of ACP, if approved, and those third parties may not perform satisfactorily for any number of reasons.

16. We rely heavily on our third-party contract research organizations as well as our clinical trial sites. They may have different priorities than we do and may fail to follow regulatory requirements, including good laboratory practice, good clinical practice and other data integrity requirements.

17. We plan to explore collaboration opportunities for the further development and potential commercialization of ACP in one or more territories outside the United States. We may not be able to enter into a collaboration on favorable terms, or at all. Even if we are able to do so, the collaboration may not be successful.

18. We rely on patents to protect our proprietary position. We may not obtain the patent rights that we seek and/or we may not be able to exclude our competitors from relevant markets. We may be subject to litigation involving our patents or those of third parties.

19. We are highly dependent on our information security systems and those of third parties we work with. A cybersecurity incident may cause interruptions to the progress of our operations, financial or regulatory penalties and/or harm to our reputation.

20. We rely on a limited number of employees to conduct our operations, including supervising our outside vendors. The skills needed to advance our research and development programs and plan for commercialization of our product candidates are highly specialized. We are hiring additional qualified personnel, including sales force personnel, to support the growth of our business. Hiring these personnel and retaining existing employees may be challenging.

21. We and any potential commercialization partners are subject to numerous healthcare laws and regulations governing our relationships with patients, healthcare professionals and third-party payors. Failure to comply with these requirements may adversely affect our business.

22. The reimbursement and payment regime for pharmaceutical products in the United States remains in flux. There are ongoing, and often bipartisan, efforts to reduce the prices of pharmaceutical products.

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 treatments for retinal diseases with significant unmet medical needs. We are committed to having a positive impact on patients' lives by delivering high-quality, safe and effective treatments designed to address debilitating retinal diseases, including earlier stages of age-related macular degeneration, or AMD.

Our lead asset is our clinical stage product candidate avacincaptad pegol, which is also referred to as ACP or Zimura®, a complement C5 inhibitor. We are currently targeting the following diseases with ACP:

- Geographic Atrophy, or 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;
- intermediate AMD, which is an earlier stage of AMD; and
- autosomal recessive Stargardt disease, or STGD1, which is an orphan inherited condition characterized by progressive damage to the central portion of the retina, or the macula, and other retinal tissue, leading to loss of vision.

In October 2019, we announced positive 12-month data for GATHER1, our first Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD. In GATHER1, 286 patients were randomized to receive various doses of ACP, including ACP 2 mg, or sham control. We observed a 27.7% (p-value = 0.0063) reduction in the mean rate of growth (slope) estimated based on GA area between the ACP 2 mg group and the corresponding sham control group over 12 months, when performing the primary analysis, and a 35.4% (p-value = 0.0050) reduction in the mean rate of growth (slope) estimated based on GA area between the two groups over 12 months, when performing the supportive analysis. These results are based on an analysis of the primary efficacy endpoint required by the U.S. Food and Drug Administration, or FDA, in accordance with our Special Protocol Assessment, or the SPA, which we describe further below. We analyzed the endpoint by using the square root transformation of the GA area, which we refer to as the primary analysis, and we analyzed the endpoint by using the observed GA area (without square root transformation), which we refer to as the supportive analysis. In GATHER1, through month 12, we did not observe any events of endophthalmitis or ischemic optic neuropathy events, and only one case of intraocular inflammation, which was mild and transient and reported as related to the injection procedure. The incidence of choroidal neovascularization, or CNV, in the study eye through month 12 was 6 patients (9.0%) in the ACP 2 mg group and 3 patients (2.7%) in the corresponding sham control group.

In June 2020, we started enrolling patients in GATHER2, our second Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD. In July 2021, we received a written agreement from the FDA under the SPA for the overall design of GATHER2. The SPA is a procedure by which the FDA provides a clinical trial sponsor with an official evaluation and written guidance on the design of a proposed protocol intended to form the basis for a new drug application, or NDA. In connection with our SPA, the FDA recommended, and we accepted, modifying the primary efficacy endpoint for the GATHER2 trial from the mean rate of change in GA area over 12 months measured by fundus autofluorescence, or FAF, at three timepoints: baseline, month 6 and month 12, to the mean rate of growth (slope) estimated based on GA area measured by FAF in at least three timepoints: baseline, month 6 and month 12.

In September 2022, we announced positive 12-month top-line data for GATHER2. In GATHER2, 448 patients were randomized on a 1:1 basis to receive ACP 2 mg or sham control over the first 12 months of the trial. At 12 months, we measured the primary efficacy endpoint in accordance with the SPA. In GATHER2, we observed a 14.3% (p-value = 0.0064) reduction in the mean rate of growth (slope) in GA area between the two groups at 12 months with the primary analysis, and a 17.7% (p-value = 0.0039) reduction in the mean rate of growth (slope) in GA area between the two groups at 12 months with the supportive analysis. We did not observe any events of endophthalmitis, intraocular inflammation events, events of vasculitis or ischemic optic neuropathy events through month 12, and the incidence of CNV in the study eye through month 12 was 15 patients (6.7%) in the ACP 2 mg group and 9 patients (4.1%) in the sham control group.

We believe that with the statistically significant results from our GATHER1 and GATHER2 trials and the safety profile of ACP to date, we have sufficient data from two independent, adequate and well-controlled pivotal clinical trials of ACP in GA secondary to AMD to support an application for marketing approval. In November 2022, the FDA granted breakthrough therapy designation to ACP for the treatment of GA secondary to AMD. In December 2022, we completed the rolling submission of our NDA to the FDA for marketing approval of ACP for the treatment of GA secondary to AMD. In February 2023, the FDA accepted our NDA for filing and granted priority review with a Prescription Drug User Fee Act, or PDUFA, target action date of August 19, 2023.

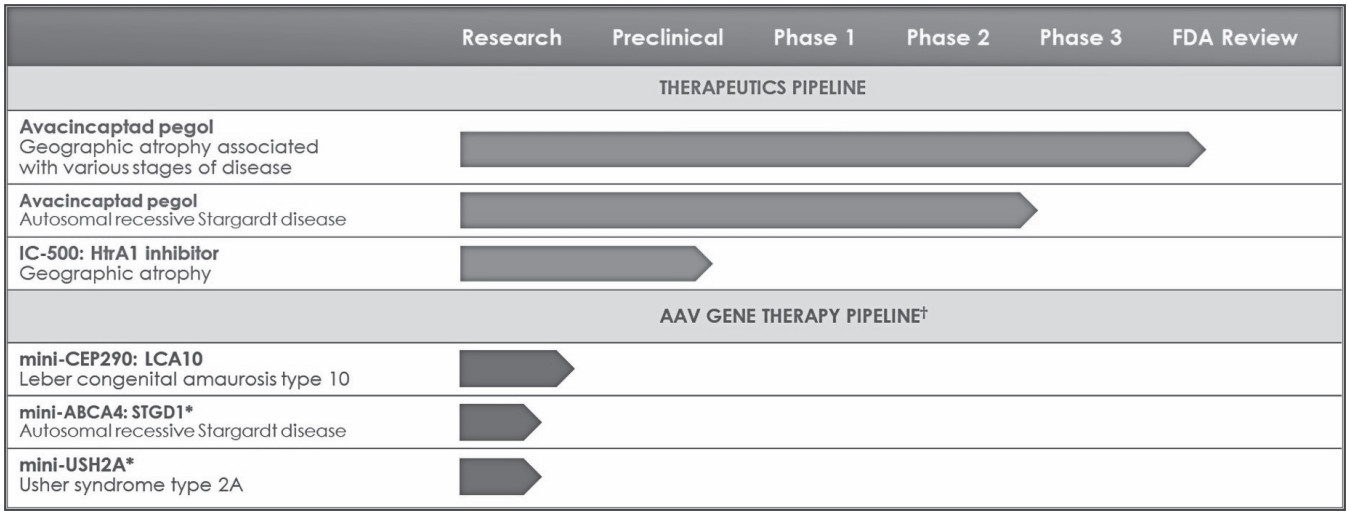
In addition to ACP, we are developing our preclinical product candidate IC-500, a High temperature requirement A serine peptidase 1 protein, or HtrA1, inhibitor, for GA secondary to AMD and potentially other age-related retinal diseases. Based on current timelines and subject to successful preclinical development and current good manufacturing practices, or cGMP, manufacturing, we expect to submit an investigational new drug application, or IND, to the FDA for IC-500 during the first half of 2024.

Our portfolio also includes several ongoing gene therapy research programs, each of which uses adeno-associated virus, or AAV, for gene delivery. These AAV mediated gene therapy programs are targeting the following orphan inherited retinal diseases, or IRDs:

- Leber Congenital Amaurosis type 10, or LCA10, which is characterized by severe bilateral loss of vision at or soon after birth;
- STGD1; and
- IRDs associated with mutations in the USH2A gene, which include Usher syndrome type 2A, or Usher 2A, and USH2A-associated non-syndromic 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.



† In December 2022, we assigned the rights to our licenses to IC-100 (RHO-adRP) and IC-200 (BEST1-related IRDs) to Opus Genetics.
*We have an option to exclusively in-license intellectual property resulting from these programs.

2022 Highlights

- In 2022, we achieved a number of significant company milestones, including the following:
- In September 2022, we announced positive 12-month data from the GATHER2 trial. We achieved a 12-month injection fidelity rate of 92.5% for the GATHER2 trial.
- In November 2022, the FDA granted breakthrough therapy designation for ACP for the treatment of GA secondary to AMD.
- In December 2022, we completed the rolling submission of our NDA to the FDA for marketing approval of ACP for the treatment of GA secondary to AMD.
- In June 2022, we entered into an exclusive license agreement with DelSiTech Ltd., or DelSiTech, for worldwide development and commercialization rights to its silica based sustained release delivery technology for use with ACP.
- In July 2022, we entered into a Loan and Security Agreement with Hercules Capital Inc. and Silicon Valley Bank, or the Loan Agreement, providing up to $250.0 million in term loans, or the 2022 Term Loan Facility.

- In December 2022, we closed an underwritten public offering in which we sold 15,352,500 shares of our common stock and raised approximately $324.3 million in net proceeds, after deducting underwriting discounts and commissions and other offering expenses.

- We continued to hire strategically to support key areas of our business, with a total of 74 full-time employees joining our team over the course of 2022.

Business Development and Financing Activities

As we prepare for the potential marketing approval and potential commercial launch of ACP, progress our research and development programs and evaluate our overall strategic priorities, we continue to pursue selective business development and financing opportunities that advance us toward our strategic goals. We plan to continue to evaluate, on a selective and targeted basis, opportunities to obtain rights to additional product candidates and technologies for retinal diseases, with a focus on additional sustained release delivery technologies for ACP. In addition, we plan to explore potential collaboration opportunities for the future development and potential commercialization of ACP in one or more territories outside the United States.

Please see later in this Business section for information about our exclusive license agreement with DelSiTech for its sustained release delivery technology for ACP and our asset purchase agreement with Opus Genetics Inc., or Opus, for our former preclinical stage gene therapy product candidates, IC-100 and IC-200.

For information about the 2022 Term Loan Facility with Hercules Capital and Silicon Valley Bank and our follow-on public offering completed in December 2022, please see the Liquidity and Capital Resources section of Management' s Discussion and Analysis of Financial Condition and Results of Operations set forth in Part I, Item 7 of this Annual Report on Form 10-K. We believe we have sufficient financial resources to launch ACP for GA in the United States, if approved based on our expectations. We plan to continue to pursue capital raising transactions when they are available on terms 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 and 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, including Geographic Atrophy and intermediate AMD

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 paper published in *Eye and Vision* and a 2014 paper published in *The Lancet*, we expect that by 2050 approximately 22 million individuals in the United States will have a form of AMD and that by 2040 approximately 288 million individuals worldwide will 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 nearly double to approximately 88 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, which generally become larger and more numerous as AMD progresses. 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. A 2022 review in the *American Academy of Ophthalmology* estimates that

approximately 80% of AMD patients have the dry 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. Many individuals with GA experience dark spots in their field of vision, referred to as scotoma, even if their central vision remains normal. As a result, 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 epidemiology studies published in 2004 in *Archives of Ophthalmology* and in 2011 *JAMA Ophthalmology,* we estimate that there are currently approximately 1.6 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 multiple anti-VEGF therapies are available for treatment of wet AMD, as of February 2023 there is only one FDA approved treatment for GA.

Before the development of central GA or wet AMD, many AMD patients experience a less advanced form of the disease, commonly referred to as intermediate AMD. Intermediate AMD is typically characterized by the presence of extensive medium-size drusen (between 63 μm and 125 μm in height) and/or one or more large drusen (larger than 125 μm in height). While most of these patients have well preserved best corrected visual acuity, or BCVA, and are otherwise asymptomatic, many experience other visual disturbances such as blurred vision while reading or difficulty with adapting to seeing in low light.

The absence of treatment options for GA and many other stages of AMD, including intermediate 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 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.

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 nonsyndromic autosomal recessive retinitis pigmentosa. Usher 2A is an autosomal recessive syndrome characterized by hearing loss from birth and progressive vision loss, due to RP, which begins in adolescence or adulthood. *USH2A*-associated nonsyndromic 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 nonsyndromic autosomal recessive retinitis pigmentosa.

Avacincaptad pegol (ACP)

We are currently developing our product candidate ACP, a C5 complement inhibitor, for the treatment of GA and STGD1. ACP 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. ACP 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.

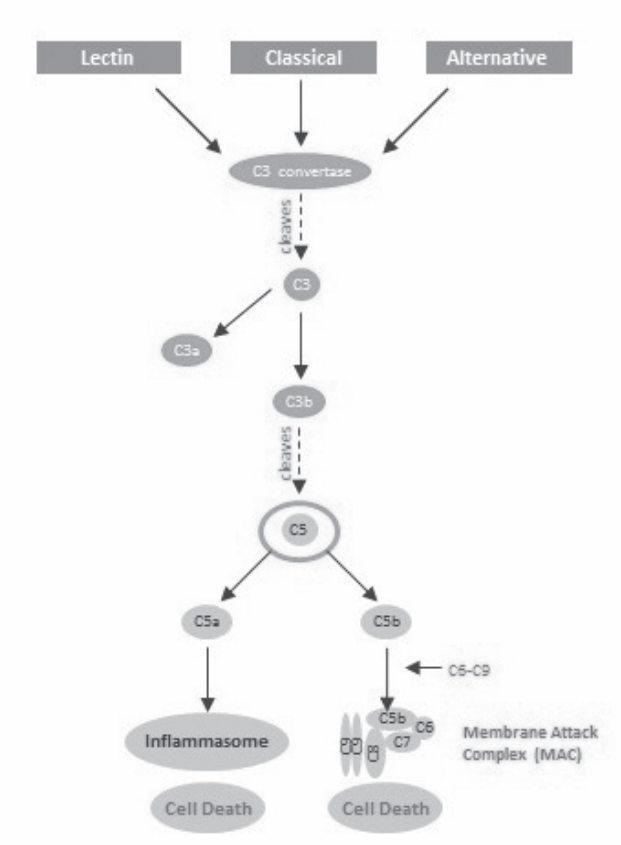
The Complement System and Its Potential Role in AMD and STGD1

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 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. A study published in *Nature Communications* in 2021 used patient-derived induced pluripotent stem cells to show that local activation of the complement system could induce drusen formation in RPE cells and that the inhibition of C5a could mitigate AMD-like pathology in the RPE cells. 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.

ACP 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, ACP 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 various stages of AMD and STGD1.

Our ACP Clinical Programs

The following is a brief description of the completed GATHER1 trial and the ongoing GATHER2 and STAR trials and the open label extension study, and their current status:

- **GATHER1** (also known as OPH2003; GA secondary to AMD - completed): an international, randomized, double-masked, sham controlled, multi-center Phase 2/3 clinical trial evaluating the safety and efficacy of ACP for the treatment of GA secondary to AMD. We enrolled 286 patients in this trial across multiple treatment groups, including various ACP doses and sham control groups, and patients were treated and followed for 18 months. In October 2019, we announced positive 12-month data from this trial and in June 2020, we completed this trial and announced 18-month data from this trial, which supported the 12-month data.

- **GATHER2** (also known as ISEE2008; GA secondary to AMD - ongoing): an international, randomized, double-masked, sham controlled, multi-center Phase 3 clinical trial evaluating the safety and efficacy of ACP for the treatment of GA secondary to AMD. We enrolled 448 patients in this trial, who were randomized on a 1:1 basis into either a treatment group with monthly intravitreal injections of ACP 2 mg or a sham control group. As agreed to with the FDA in connection with the SPA, the primary efficacy endpoint is the mean rate of growth (slope) estimated based on GA area measured by FAF in at least three timepoints: baseline, month 6 and month 12. In September 2022, we announced positive 12-month data from this trial. We plan to treat and follow patients for 24 months in total.

- **ISEE2009** (also known as the OLE study; open label extension study - ongoing): an international, open label, multicenter study evaluating the safety of ACP 2 mg for patients who completed their month 24 visits in the GATHER2 trial. We are continuing to enroll patients.

- **STAR (**also known as OPH2005; STGD1 - ongoing): an international, randomized, double-masked, sham controlled, multi-center Phase 2b clinical trial evaluating the safety and efficacy of ACP for the treatment of STGD1. We initially enrolled 95 patients in this trial, none of whom have remaining study visits. In July 2020, we reopened enrollment in this trial in the United States. We continue to enroll patients and plan to enroll approximately 25 additional patients, with the goal of enrolling a total of approximately 120 patients. We have been and will remain masked until results are analyzed for all the patients in this trial.

In addition to the GATHER1 trial, we have completed multiple clinical trials evaluating various doses of ACP in age-related retinal diseases, including:

- OPH2001, a Phase 1/2a clinical trial of various doses of ACP for the treatment of GA, with a total of 47 patients enrolled;

- OPH2000: a Phase 1/2a clinical trial of various doses of ACP administered in combination with Lucentis® (ranibizumab), an anti-vascular endothelial growth factor, or anti-VEGF, agent, for the treatment of wet AMD, with a total of 60 patients enrolled;

- OPH2007, a Phase 2a clinical trial of various doses of ACP administered in combination with Lucentis for the treatment of wet AMD, with a total of 64 patients enrolled and treated; and

- OPH2002: a very small Phase 2a clinical trial of ACP in combination with anti-VEGF agents for the treatment of idiopathic polypoidal choroidal vasculopathy, or IPCV, in patients for whom anti-VEGF monotherapy had failed.

ACP 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 before and after each intravitreal injection. Certain of the dosing regimens we are evaluating in STAR 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 ACP clinical experience to date is described in greater detail below.

ACP - GA Trials

GATHER1: Completed Clinical Trial Assessing the Safety and Efficacy of Various Doses of ACP for GA Secondary to AMD

In October 2019, we announced 12-month data from the GATHER1 trial and in June 2020, we completed and announced 18-month data from this trial. The primary efficacy analysis was performed at the 12-month time point. Pursuant to the clinical trial protocol, patients continued to be treated and followed through month 18. We remained masked regarding the treatment group to which each individual patient was randomized throughout the duration of the trial. Following the conclusion of the trial, we have continued to review and analyze the unmasked, individual patient data from this trial.

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	ACP 1 mg	ACP 2 mg	Sham
Patients	26	25	26

In Part 1 of the trial, ACP 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 ACP 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	ACP 2 mg	ACP 4 mg	Sham
Patients	42	83	84

In Part 2 of the trial, patients in the ACP 2 mg group received one intravitreal injection of ACP 2 mg and one sham injection at each monthly visit; patients in the ACP 4 mg group received two intravitreal injections of ACP 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 ACP 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 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 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 is 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, at the time of the modifications, 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 GATHER1 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 ACP 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	**ACP 1 mg** (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 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 Hyperautofluorescence (%)	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 Data

12-Month Safety Data

Based on our review of the safety data to date, ACP 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 ACP-related adverse events, no cases of ACP-related intraocular inflammation, no cases of ACP-related increased intraocular pressure, no cases of endophthalmitis, and no discontinuations attributed by investigators to ACP 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		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 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 (ACP or sham) are set forth in the table below:

Reported Systemic TEAEs Related to ACP or Sham

	Part 1			Part 2		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 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		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 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 (ACP or sham) is set forth in the table below:

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

	Part 1			Part 2		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 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 ACP 1 mg group, 6 patients (9.0%) in the ACP 2 mg group, and 8 patients (9.6%) in the ACP 4 mg group.

Statistical Analysis for Efficacy Measures

GATHER1 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 GATHER1 trial for both the ACP 2 mg and ACP 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 GATHER1 trial regarding the comparison of ACP 2 mg to sham control is provided by data from both Part 1, with a 1:1 randomization ratio of patients receiving ACP 2 mg (25 patients) and sham (26 patients), as well as data from Part 2, with a 1:2 randomization ratio of patients receiving ACP 2 mg (42 patients) and sham (84 patients), for a total of 67 patients receiving ACP 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 ACP 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 ACP 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 ACP 2 mg should be comparable to the 84 patients receiving sham. The efficacy of ACP 2 mg was therefore evaluated through an analysis which included a regression factor by trial part. The statistical analysis for the ACP 4 mg group as compared to sham compares data for patients from Part 2 of the trial only. Data from patients receiving ACP 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 ACP 2 mg and ACP 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	ACP 2 mg (N = 67)	Sham 2 mg (N = 110)	ACP 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 ACP 1 mg group (7.7% withdrawals), 12 patients were from the combined ACP 2 mg group (17.9% withdrawals), 25 patients were from the ACP 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 GATHER1 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 GATHER1 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 ACP 2 mg and ACP 4 mg groups. The difference between the ACP treatment groups and the corresponding sham groups, in terms of mean change of square root of GA growth, was 0.11 mm for the ACP 2 mg group and 0.12 mm for the ACP 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 ACP treatment group, while missing values in the ACP 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 ACP 2 mg and ACP 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 ACP 2 mg and ACP 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 GATHER1 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	ACP 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)]	0.11	0.0072[(c)]	27.38%
Cohort	ACP 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 ACP 2 mg as compared to Sham 2 mg was adjusted for the fact that this dose of ACP 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		ACP 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		ACP 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 ACP 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 ACP 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 GATHER1 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 GATHER1, the results for the primary efficacy endpoint observed for both the ACP 2 mg and ACP 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.

Observed GA Data (non-square root transformation)

In addition to analyzing the mean rate of change in GA area at month 12 using the square root transformation of the GA area (measured in millimeters (mm)), we also analyzed the mean rate of change in GA area using the observed GA area (without the square root transformation, measured in square millimeters (mm^2)), with the MRM model. This descriptive analysis was also part of the prespecified statistical analysis plan for this trial. The observed mean GA area data for the ACP 2 mg and ACP 4 mg groups as compared to the corresponding sham control groups are summarized in the following table:

Mean Rate of Change in GA Area from Baseline to Month 12

(MRM Analysis) (Observed)

Cohort	ACP 2 mg (N = 67)	Sham 2 (N = 110)	**Difference**	**% Difference**
Mean Change in GA[(a)] (mm^2)	1.592[(b)]	2.290[(b)]	0.697	30.45%
Cohort	ACP 4 mg (N = 83)	Sham (N = 84)	**Difference**	**% Difference**
Mean Change in GA[(a)] (mm^2)	2.061	2.77	0.709	25.59%

(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.

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 ACP 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 GATHER1 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	ACP 2 mg (N = 67)	Sham 2 mg (N = 110)	Difference
Mean Change in BCVA[a]	-7.90[b]	-9.29[b]	1.39

Cohort	ACP 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	ACP 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	ACP 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.

ACP 1 mg 12-Month Efficacy Data

Efficacy data from patients receiving ACP 1 mg was not part of the prespecified statistical analysis. The total number of patients randomized to the ACP 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 ACP 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 ACP 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	ACP 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 ACP 1 mg group is small, we believe the apparent reduction in mean percentage change in GA area from baseline to month 12 in the ACP 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 ACP 2 mg and ACP 4 mg groups as compared to their corresponding sham control groups, suggest a potential dose response relationship across treatment groups.

18-Month Data

The primary purpose of the 18 month time point was to gather additional safety data. This trial was not designed to assess, and the prespecified statistical analysis plan for the trial did not include assessing, the statistical significance of the 18 month efficacy data for the treatment groups as compared to the corresponding sham control groups. The reduction in the mean rate of GA growth over 18 months was 28.11% for the ACP 2 mg group as compared to the corresponding sham control group and 29.97% for the ACP 4 mg group as compared to the corresponding sham control group. The descriptive p-values for the treatment effects at month 18 were p=0.0014 for the ACP 2 mg group and p=0.0021 for the ACP 4 mg group. The analysis of the 18-month efficacy data is descriptive only.

GA Growth Data over 18 Months

The mean rate of change in GA growth over 18 months was measured by FAF based on readings at four time points (baseline, month 6, month 12 and month 18) and was calculated using the square root transformation of the GA area. The FAF images were assessed by an independent masked reading center. The prespecified statistical analysis plan used MRM to compare data for the ACP 2 mg and ACP 4 mg groups to the corresponding sham groups. Detailed data are shown below (the p-values for the 18 month statistical analyses are descriptive in nature):

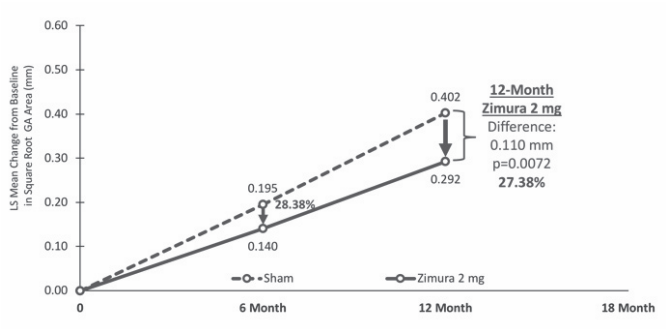
Mean Rate of Change in Geographic Atrophy (GA) Area from Baseline to Month 18
(Square Root Transformation)

Cohort	ACP 2 mg (N = 67)	Sham (N = 110)	Difference	% Difference	P-Value (Descriptive)
Mean Change in GA[(a)] (mm)	0.430	0.599	0.168	28.11%	0.0014
Cohort	**ACP 4 mg (N = 83)**	**Sham (N = 84)**	**Difference**	**% Difference**	**P-Value (Descriptive)**
Mean Change in GA[(b)] (mm)	0.391	0.559	0.167	29.97%	0.0021

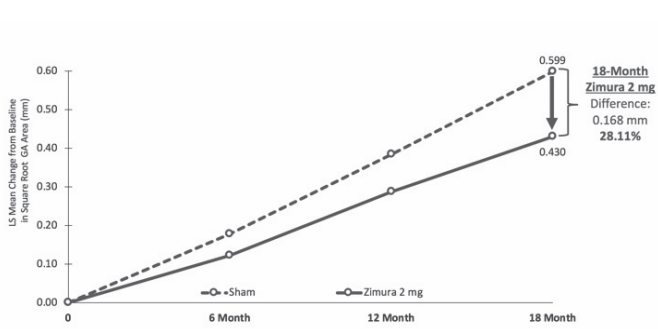
(a) Based on least squares means from MRM model, drawing on all available data at the month 18 time point, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data.
(b) These least squares means are estimates of the MRM model, drawing on all available data, at the month 18 time point.

The graphs below illustrate the difference in mean rate of GA growth between each of the ACP 2 mg and ACP 4 mg treatment groups and their corresponding sham control groups based on the MRM analysis at both 12 months and 18 months.

Primary Efficacy Endpoint Met at 12 Months
ACP 2 mg vs Sham
(Square Root Transformation)

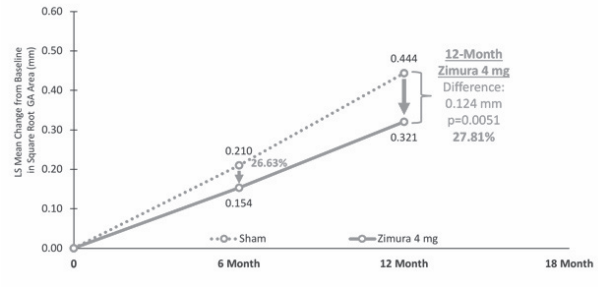


Decrease in GA Growth Over 18 Months
ACP 2 mg vs Sham
(Square Root Transformation)

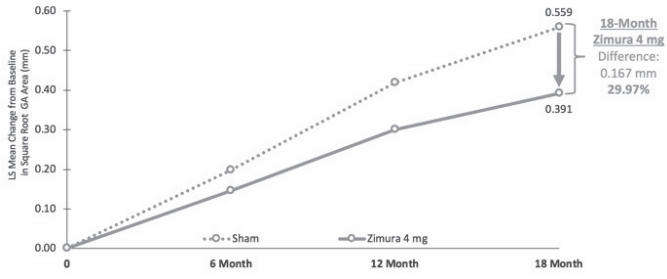


ITT Population; Based on the least squares means from MRM model drawing on all available data at the respective 12 month and 18 month analysis time points, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data; Hochberg procedure used for significance testing for 12 month data.

Primary Efficacy Endpoint Met at 12 Months
ACP 4 mg vs Sham
(Square Root Transformation)



Decrease in GA Growth Over 18 Months
ACP 4 mg vs Sham
(Square Root Transformation)



ITT Population; Based on the least squares means from the MRM model drawing on all available data at the respective 12 month and 18 month analysis time points; Hochberg procedure used for significance testing for 12 months data.

18-Month ACP 2 mg GA Data by Part

Consistent with the analysis performed at 12 months, the analysis of the mean change in GA growth for ACP 2 mg as compared to the corresponding sham control group over 18 months was adjusted for the fact that this dose of ACP was tested in both Part 1 and Part 2 of the trial, each of which had different randomization ratios.

The least squares mean changes in GA in Part 1 and Part 2 at month 18 are shown separately in the following table:

Mean Rate of Change in GA Area from Baseline to Month 18
(MRM Analysis) (Square Root Transformation)

Cohort		ACP 2 mg (N = 25)	Sham (N = 26)	Difference	% Difference
Part 1	Mean Change in GA[(a)] (mm)	0.464	0.635	0.170	26.84%

(a) Based on the least squares mean from the MRM model.

Cohort		ACP 2 mg (N = 42)	Sham (N = 84)	Difference	% Difference
Part 2	Mean Change in GA[(a)] (mm)	0.440	0.608	0.168	27.67%

(a) Based on the least squares means from the MRM model.

When the data for the ACP 2 mg groups from each Part of the trial as compared to the corresponding sham control groups are analyzed using the MRM model, which includes a regression factor by part, the mean difference in GA growth over 18 months between the ACP 2 mg and sham control groups is 0.168 mm, representing a 28.11% relative benefit in the ACP 2 mg group as compared to the corresponding sham control group.

Observed 18-Month GA Data (non-square root transformation)

In addition to analyzing the mean rate of change in GA area at month 18 using the square root transformation of the GA area (measured in millimeters (mm)), we also analyzed the mean rate of change in GA area using the observed GA area (without the square root transformation, measured in square millimeters (mm^2)), with the MRM model. This descriptive

analysis was also part of the prespecified statistical analysis plan for this trial. The observed mean GA area data for the ACP 2 mg and ACP 4 mg groups as compared to the corresponding sham control groups are summarized in the following table:

Mean Rate of Change in GA Area from Baseline to Month 18

(MRM Analysis) (Observed)

Cohort	ACP 2 mg (N = 67)	Sham 2 (N = 110)	Difference	% Difference
Mean Change in GA[(a)] (mm^2)	2.431[(b)]	3.587[(b)]	1.156	32.24%

Cohort	ACP 4 mg (N = 83)	Sham (N = 84)	Difference	% Difference
Mean Change in GA[(a)] (mm^2)	2.460	3.486	1.026	29.44%

(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.

18-Month Visual Acuity Data

In addition to analyzing mean change in GA area, we also performed pre-specified analyses of the mean change in BCVA from baseline to month 18 and the mean change in LL BCVA from baseline to month 18, 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 ACP treatment groups was not clinically different from the sham control groups.

The GATHER1 trial was not designed to reliably assess differences in mean changes in BCVA or LL BCVA with statistical significance. Data for the mean change in BCVA and LL BCVA at month 18 are summarized in the following tables:

Mean Change in BCVA from Baseline to Month 18

(MRM Analysis) (ETDRS letters)

Cohort	ACP 2 mg (N = 67)	Sham (N = 110)	Difference
Mean Change in BCVA[(a)]	-12.7[(b)]	-15.1[(b)]	2.37

Cohort	ACP 4 mg (N = 83)	Sham (N = 84)	Difference
Mean Change in BCVA[(a)]	-4.27	-7.07	2.80

(a) Based on the least squares mean from the MRM model.
(a) 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 18

(MRM Analysis) (ETDRS letters)

Cohort	ACP 2 mg (N = 67)	Sham (N = 110)	Difference
Mean Change in LL BCVA[(a)]	-2.72[(b)]	-3.10[(b)]	0.37

Cohort	ACP 4 mg (N = 83)	Sham (N = 84)	Difference
Mean Change in LL BCVA[(a)]	2.85	1.68	1.17

(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.

ACP 1 mg 18-Month Efficacy Data

We performed descriptive analyses on the 18 month data for patients in the ACP 1 mg group as compared to the patients in the sham control group in Part 1 of the trial.

The mean rate of change in GA area for the ACP 1 mg group and the corresponding sham group from Part 1 of the trial over 18 months is summarized in the following table:

Summary of GA Area (mm) and Mean Percentage Change from Baseline to Month 18
(Square Root Transformation)

Cohort	ACP 1 mg (N = 26)	Sham (N = 26)
Mean Sq. Root of GA at BL, mm	2.591	2.623
Mean Sq. Root of GA at M18, mm	3.258	3.230
Difference	0.667	0.607
Mean % Change[(a)]	21.91%	23.87%

BL = Baseline; M18 = Month 18
(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 ACP 1 mg group is small, we believe the apparent reduction in mean percentage change in GA area from baseline to month 18 in the ACP 1 mg group as compared to the sham control group, when compared with the results observed in the ACP 2 mg and ACP 4 mg groups as compared to their corresponding sham control groups, may suggest a potential dose response relationship across treatment groups.

18-Month Safety Data

Based on our review of the safety data in the trial, ACP was generally well tolerated after 18 months of administration. During the trial, there were no investigator-reported ACP-related adverse events, no ACP-related intraocular inflammation, no ACP-related increased intraocular pressure, no cases of endophthalmitis, and no discontinuations attributed by investigators to ACP in the trial. Through month 18, the reported incidence of CNV in the untreated fellow eye was 11 patients (3.8%), and in the study eye was 3 patients (2.7%) in the sham control group, 2 patients (7.7%) in the ACP 1 mg group, 8 patients (11.9%) in the ACP 2 mg group, and 13 patients (15.7%) in the ACP 4 mg group. The most frequently reported ocular adverse events were related to the injection procedure. The numbers below are based on investigator-reported adverse events occurring during the 18-month duration of the trial for all patients.

The number of patients with one or more serious TEAEs organized by MedDRA system organ class are set forth in the table below:

Patients with One or More Serious TEAEs in Any Organ Class

	Part 1			Part 2		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Blood and lymphatic system disorders	0	0	0	0	1 (1.2%)	0
Cardiac disorders	1 (3.8%)	0	1 (3.8%)	1 (2.4%)	2 (2.4%)	3 (3.6%)
Eye disorders	0	0	0	1 (2.4%)	1 (1.2%)	0
Gastrointestinal disorders	1 (3.8%)	1 (4.0%)	2 (7.7%)	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	2 (4.8%)	8 (9.6%)	2 (2.4%)
Injury, poisoning and procedural complications	0	1 (4.0%)	1 (3.8%)	1 (2.4%)	3 (3.6%)	2 (2.4%)
Metabolism and nutrition disorders	0	0	2 (7.7%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (3.8%)	0	0	0	0	3 (3.6%)
Benign, malignant and unspecified neoplasms (including cysts and polyps)	0	0	1 (3.8%)	1 (2.4%)	1 (1.2%)	3 (3.6%)
Nervous system disorders	1 (3.8%)	1 (4.0%)	2 (7.7%)	2 (4.8%)	3 (3.6%)	2 (2.4%)
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%)	5 (6.0%)
Vascular disorders	0	0	0	0	0	1 (1.2%)

Of the reported serious TEAEs that were eye disorders, one TEAE was an ischemic optic neuropathy (in the ACP 2 mg group) and one TEAE was a retinal detachment (in the ACP 4 mg group). Neither of these TEAEs were reported as related to ACP.

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

Reported TEAEs Related to ACP or Sham

	Part 1			Part 2		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 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		
	ACP 1 mg (N = 26)	**ACP 2 mg** (N = 25)	**Sham** (N = 26)	**ACP 2 mg** (N = 42)	**ACP 4 mg** (N = 83)	**Sham 4 mg** (N = 84)
Eye disorders	12 (46.2%)	11 (44.0%)	6 (23.1%)	28 (66.7%)	61 (73.5%)	39 (46.4%)
Eye disorders related to injection procedure	4 (15.4%)	5 (20.0%)	2 (7.7%)	18 (42.9%)	46 (55.4%)	24 (28.6%)

The number of patients with one or more ocular TEAEs in the study eye, identified by the investigator as related to the study drug (ACP or sham) is set forth in the table below:

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

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

In addition to us collecting investigator-reported adverse events, the independent masked reading center performed multi-modal imaging analysis. Multi-modal imaging analysis is a process used to assess patient retinal findings by reviewing different image types, in this case optical coherence tomography, or OCT, images and fluorescein angiography, to provide a more comprehensive view of the patient's retinal tissue. OCT is an ultra-high resolution imaging technology commonly used to visualize the retinal tissue. OCT is capable of rendering images in multiple dimensions and from multiple perspectives, and is an imaging technique commonly used by retinal specialists to diagnose, treat and follow patients with CNV. Fluorescein angiography is a technique that involves injection of a fluorescent dye into the systemic circulation and capturing images showing the circulating dye during transit through the retinal circulation using a specialized camera. In this trial, the reading center's multi-modal imaging analysis identified one additional case of macular CNV for a patient in the ACP 4 mg group at month 12. Because this patient's investigator did not detect the CNV, the patient remained in the trial through month 18.

Post-hoc Analysis of GATHER1 Data using the FDA Required Analysis of Primary Efficacy Endpoint

In parallel discussions with those for the GATHER2 SPA, the FDA indicated that, as part of a future NDA for ACP, the results from GATHER1 will be considered using the original prespecified primary efficacy endpoint analysis, as described above, together with a post-hoc analysis using the same FDA-preferred method that will be used for the GATHER2 trial (mean rate of growth (slope) estimated based on GA area measured by FAF in the relevant timepoints). The 12 month and 18 month results of this post-hoc analysis, as compared to the results of the original prespecified analysis for GATHER1, for the ACP 2 mg and ACP 4 mg treatment arms as compared to their corresponding sham arms, are described below. Safety results from GATHER1 were not impacted as part of this analysis.

ACP 2 mg Data

MRM Analysis	**ACP 2 mg (N = 67)**	**Sham (N = 110)**	**Difference**	**% Difference**	**P-Value**
12 Month Sq. Rt. Transformation:					
Mean Rate of Change in GA Area (mm)	0.292	0.402	0.110	27.38%	0.0072[(a)]
Mean Rate of GA Growth (Slope) (mm)	0.283	0.392	0.109	27.73%	0.0063[(b)]
12 Month Observed Data:					
Mean Rate of Change in GA Area (mm^2)	1.592	2.29	0.697	30.45%	0.0059[(b)]
Mean Rate of GA Growth (Slope) (mm^2)	1.221	1.889	0.668	35.37%	0.0050[(b)]
18 Month Sq. Rt. Transformation:					
Mean Rate of Change in GA Area (mm)	0.430	0.599	0.168	28.11%	0.0014[(b)]
Mean Rate of GA Growth (Slope) (mm)	0.451	0.607	0.156	25.75%	0.0027[(b)]
18 Month Observed Data:					
Mean Rate of Change in GA Area (mm^2)	2.431	3.587	1.156	32.24%	0.0009[(b)]
Mean Rate of GA Growth (Slope) (mm^2)	1.914	2.951	1.037	35.13%	0.0023[(b)]

Explanatory notes:

- the estimates for the ACP 2 mg group vs. sham are from the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2 of the trial, and should not be interpreted as directly observed data;

(a) indicates prespecified primary endpoint; statistically significant;

(b) indicates descriptive p-value.

ACP 4 mg Data

MRM Analysis	ACP 4 mg (N = 83)	Sham (N = 84)	Difference	% Difference	P-Value
12 Month Sq. Rt. Transformation:					
Mean Rate of Change in GA Area (mm)	0.321	0.444	0.124	27.81%	0.0051[(a)]
Mean Rate of GA Growth (Slope) (mm)	0.307	0.416	0.109	26.31%	0.0100[(b)]
12 Month Observed Data:					
Mean Rate of Change in GA Area (mm^2)	2.061	2.770	0.709	25.59%	0.0082[(b)]
Mean Rate of GA Growth (Slope) (mm^2)	1.674	2.273	0.599	26.34%	0.0147[(b)]
18 Month Sq. Rt. Transformation:					
Mean Rate of Change in GA Area (mm)	0.391	0.559	0.167	29.97%	0.0021[(b)]
Mean Rate of GA Growth (Slope) (mm)	0.373	0.512	0.139	27.11%	0.0086[(b)]
18 Month Observed Data:					
Mean Rate of Change in GA Area (mm^2)	2.460	3.486	1.026	29.44%	0.0034[(b)]
Mean Rate of GA Growth (Slope) (mm^2)	2.142	3.010	0.868	28.82%	0.0106[(b)]

Explanatory notes:

[(a)] indicates prespecified primary endpoint; statistically significant;

[(b)] indicates descriptive p-value.

ACP 2 mg Data by Part

As previously discussed, we enrolled patients for the GATHER1 trial in two different parts, Part 1 and Part 2, with different dosages and randomization ratios in each Part. Twenty-five patients receiving ACP 2mg were enrolled in Part 1 of the trial and 42 patients receiving ACP 2mg were enrolled in Part 2 of the trial.

Below are the month 12 and month 18 results for the ACP 2 mg group as compared to its corresponding sham group, for both Part 1 and Part 2 of the trial, using both the original prespecified primary efficacy endpoint analysis for the GATHER1 trial and the post-hoc analysis using the FDA-preferred method that is used for the GATHER2 trial:

Part 1 Only Data

MRM Analysis	ACP 2 mg (N = 25)	Sham (N = 26)	Difference	% Difference
12 Month Sq. Rt. Transformation:				
Mean Rate of Change in GA Area (mm)	0.329	0.422	0.093	22.07%
Mean Rate of GA Growth (Slope) (mm)	0.307	0.423	0.116	27.39%
12 Month Observed Data:				
Mean Rate of Change in GA Area (mm^2)	1.910	2.593	0.683	26.35%
Mean Rate of GA Growth (Slope) (mm^2)	1.655	2.238	0.584	26.08%
18 Month Sq. Rt. Transformation:				
Mean Rate of Change in GA Area (mm)	0.464	0.635	0.170	26.84%
Mean Rate of GA Growth (Slope) (mm)	0.446	0.630	0.184	29.23%
18 Month Observed Data:				
Mean Rate of Change in GA Area (mm^2)	2.789	4.103	1.314	32.03%
Mean Rate of GA Growth (Slope) (mm^2)	2.482	3.393	0.911	26.85%

Part 2 Only Data

MRM Analysis	ACP 2 mg (N = 42)	Sham (N = 84)	Difference	% Difference
12 Month Sq. Rt. Transformation:				
Mean Rate of Change in GA Area (mm)	0.308	0.422	0.114	27.02%
Mean Rate of GA Growth (Slope) (mm)	0.303	0.424	0.121	28.51%
12 Month Observed Data:				
Mean Rate of Change in GA Area (mm^2)	1.743	2.434	0.690	28.36%
Mean Rate of GA Growth (Slope) (mm^2)	1.419	2.154	0.735	34.14%
18 Month Sq. Rt. Transformation:				
Mean Rate of Change in GA Area (mm)	0.440	0.608	0.168	27.67%
Mean Rate of GA Growth (Slope) (mm)	0.474	0.622	0.148	23.85%
18 Month Observed Data:				
Mean Rate of Change in GA Area (mm^2)	2.550	3.649	1.099	30.12%
Mean Rate of GA Growth (Slope) (mm^2)	2.203	3.264	1.061	32.51%

GATHER2: Ongoing Phase 3 Clinical Trial Assessing Safety and Efficacy of ACP 2 mg for GA Secondary to AMD

In September 2022, we announced positive 12-month data from the GATHER2 trial.

Trial Design

In this trial, we enrolled 448 patients, who were randomized into two groups: a first group receiving monthly administrations of ACP 2 mg for 12 months, and a second group receiving monthly administrations of sham. In accordance with our SPA with the FDA, the prespecified primary efficacy endpoint will be the mean rate of growth (slope) estimated based on GA area measured by FAF in at least three timepoints: baseline, month 6 and month 12. At month 12, we re-randomized patients in the ACP 2 mg arm to receive either monthly or every other month administrations of ACP 2 mg, and patients receiving monthly administrations of sham continue to receive monthly administrations of sham. We plan to treat and follow patients for 24 months in total.

The key ophthalmic inclusion criteria for GATHER2 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 GATHER1 trial, 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 GATHER1 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 GATHER1 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 GATHER2 provides that patients undergo monthly OCT imaging, and if an investigator suspects that a patient has CNV or if a patient experiences a decrease in visual acuity, as measured by a loss of more than five ETDRS letters between a visit and the immediately prior visit, the independent masked reading center will confirm whether the patient has CNV using multi-modal imaging. In the event a CNV case is confirmed, the investigator will treat the CNV with one of two anti-VEGF agents, Lucentis or Eylea® (aflibercept), in accordance with the label for that anti-VEGF agent. These patients will remain in the trial and measurements of these patients' GA are included in the primary efficacy analysis if their FAF images can be assessed by the masked reading center.

We initiated an open-label extension study for patients who completed the GATHER2 trial; information about this study is described further below.

Baseline Characteristics

We collected baseline characteristics for all patients participating in the GATHER2 trial, which are presented below for each treatment group. These baseline characteristics include the intent-to-treat, or ITT, 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. 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. Based on these data, we believe that the baseline characteristics were balanced across the treatment groups.

	Treatment Group	
Baseline Characteristic	**ACP 2 mg** (N = 225)	**Sham** (N = 222)
Mean age, years (SD)	76.3 (8.6)	76.7 (8.8)
Female gender, number (%)	154 (68.4%)	156 (70.3%)
Active smokers, number (%)	106 (47.1%)	107 (48.2%)
Caucasian race, number (%)	182 (80.9%)	186 (83.8%)
Iris color, number (%):		
Light	93 (41.3%)	109 (49.1%)
Medium	96 (42.7%)	79 (35.6%)
Dark	36 (16.0%)	34 (15.3%)
Mean intraocular pressure, mmHg (SD)	15.2 (2.5)	14.9 (2.6)
Non-subfoveal GA, number (%)	225 (100%)	222 (100%)
Multifocal GA, number (%)	178 (79.1%)	178 (80.2%)
GA size of greater than or equal to 4 disc areas, number (%)	54 (24.0%)	64 (28.8%)
Mean GA area, mm^2 (SD)	7.48 (4.01)	7.81 (3.89)
Mean Sq. Root of GA area, mm (SD)	2.641 (0.714)	2.707 (0.696)
Bilateral GA, number (%)	212 (94.0%)	210 (95.0%)
Mean BCVA, ETDRS letters (SD)	70.9 (8.9)	71.6 (9.4)
Mean LL BCVA, ETDRS letters (SD)	41.0 (19.7)	39.6 (19.6)
Patients with Hyperautofluorescence - Banded/ Diffuse, number (%)	217 (96.4%)	218 (98.2%)
Height, cm (SD)	164.6 (10.6)	164.0 (9.4)
Weight, kg (SD)	75.9 (18.3)	75.0 (15.8)

12-Month Safety Data

In GATHER2, there were no events of endophthalmitis, no intraocular inflammation events, no events of vasculitis and no ischemic optic neuropathy events through month 12. The most frequently reported ocular adverse events were related to the injection procedure, including transient intraocular pressure.

The incidence of CNV in the study eye through month 12 was 15 patients (6.7%) in the ACP 2 mg group and 9 patients (4.1%) in the sham control group. An independent masked reading center assessed the macular CNV, or MNV, cases in GATHER2 at the 12-month timepoint for exudative macular neovascularization, or eMNV, and non-exudative macular neovascularization, or neMNV (versus peripapillary neovascularization, where the neovascularization is located around the optic nerve and not encroaching on the macula). As previously disclosed, the reading center classifies cases of MNV as exudative or non-exudative based on the following OCT criteria:

- Exudative MNV, or eMNV, is MNV that presents with new onset fluid in either the subretinal space or the intraretinal space. The subretinal space is the area on OCT between the RPE and photoreceptor cells. The intraretinal space is the area on OCT containing the photoreceptors and other neurosensory cells of the retina.
- Non-exudative MNV, or neMNV, is neovascularization located in the macula but which does not present with new onset fluid in the subretinal or intraretinal spaces. In some cases, isolated fluid may be present in the sub-RPE space, which is the area between the RPE and Bruch's membrane, a layer of tissue directly beneath the RPE separating the RPE from the choroid. A case is also considered to be neMNV when the MNV may not be visible but both a double-layer sign and sub-RPE fluid are present. A double-layer sign is characterized by a shallow elevation of the RPE typically caused by the accumulation of fluid or debris in the sub-RPE space.

The following tables provide further detail on these adverse events of interest in GATHER2:

Reported Adverse Events of Interest

	Endophthalmitis	Intraocular Inflammation	Ischemic Optic Neuropathy
ACP 2mg (N=225)	0	0	0
Sham (N=222)	0	0	0

Reported Choroidal Neovascularization Cases

	eMNV (%)	neMNV (%)	Peripapillary CNV (%)	Total CNV (%)
ACP 2mg (N=225)	11 (4.9%)	1 (0.5%)	3 (1.3%)	15 (6.7%)
Sham (N=222)	7 (3.2%)	0	2 (0.9%)	9 (4.1%)

The number of patients having treatment emergent adverse events, or TEAEs, organized by MedDRA system organ class, a standard method of reporting adverse events, for which there are two percent or greater of such TEAE among the patients in any treatment group, are set forth in the table below:

Patients with TEAEs in any Organ Class for which TEAE Comprises 2% or Greater of Patients in any Treatment Group

	Treatment Group	
Organ Class	**ACP 2 mg** (N = 225)	**Sham** (N = 222)
Blood and lymphatic system disorders	4 (1.8%)	5 (2.3%)
Cardiac disorders	22 (9.8%)	16 (7.2%)
Ear and labyrinth disorders	1 (0.4%)	5 (2.3%)
Eye disorders	110 (48.9%)	84 (37.8%)
Gastrointestinal disorders	16 (7.1%)	13 (5.9%)
General disorders and administration site conditions	7 (3.1%)	10 (4.5%)
Infections and infestations	59 (26.2%)	58 (26.1%)
Injury, poisoning and procedural complications	36 (16.0%)	32 (14.4%)
Investigations	31 (13.8%)	10 (4.5%)
Metabolism and nutrition disorders	9 (4.0%)	8 (3.6%)
Musculoskeletal and connective tissue disorders	22 (9.8%)	24 (10.8%)
Benign, malignant and unspecified neoplasms (including cysts and polyps)	9 (4.0%)	16 (7.2%)
Nervous system disorders	14 (6.2%)	28 (12.6%)
Psychiatric disorders	6 (2.7%)	4 (1.8%)
Renal and urinary disorders	10 (4.4%)	5 (2.3%)
Respiratory, thoracic and mediastinal disorders	10 (4.4%)	8 (3.6%)
Skin and subcutaneous tissue disorders	8 (3.6%)	10 (4.5%)
Vascular disorders	14 (6.2%)	13 (5.9%)

The number of patients having ocular TEAEs in the study eye for which there are two percent or greater of such TEAE among the patients in any treatment group, are set forth in the table below:

Ocular TEAEs in any Organ Class in Study Eyes for which TEAE Comprises 2% or Greater of Patients in any Treatment Group

	Treatment Group	
Organ Class	**ACP 2 mg** (N = 225)	**Sham** (N = 222)
Eye disorders	104 (46.2%)	80 (36.0%)
Infections and infestations	3 (1.3%)	5 (2.3%)
Injury, poisoning and procedural complications	5 (2.2%)	1 (0.5%)
Investigations	21 (9.3%)	2 (0.9%)

Among the eye disorder ocular TEAEs, two of the TEAEs were reported as serious in the ACP 2 mg group, as compared to three TEAEs in the sham group. In the ACP 2 mg group, both serious TEAEs were cases of CNV. In the sham group, one serious TEAE was a CNV case, one was a case of visual acuity reduced and one was a case of visual acuity reduced transiently.

Among the ocular cases of injury, poisoning and procedural complications, all were procedural complications of intravitreal injection or sham administration. None of these cases were serious.

All 23 ocular investigation cases were cases of increased intraocular pressure, or IOP. None of these cases were serious. Of the 21 cases in the ACP 2 mg group, 20 of them were transient in nature; of the 20 transient cases, 19 of them resolved the same day. The single non-transient case in the ACP 2 mg group was for a patient with glaucoma at baseline. The increased incidence of increased IOP is expected for an intravitreal injection as compared to a sham procedure. Patients in the sham group had a barrel of a syringe placed against the eye to simulate the pressure of an injection but no needle penetrates the eye.

12-Month Efficacy Data

The primary efficacy endpoint, in accordance with our SPA with the FDA, is the mean rate of growth (slope) estimated based on GA area, as measured by FAF based on readings at three timepoints: baseline, month 6 and month 12. The FAF images were assessed by an independent masked reading center. We performed the pre-specified primary analysis of the endpoint by using the square root transformation of the GA area and we performed the pre-specified supportive analysis of the endpoint by using the observed GA area (without square root transformation). Detailed data for the primary efficacy endpoint with both the primary analysis and supportive analysis are shown in the accompanying table:

Mean Rate of Growth (Slope) in GA Area from Baseline to Month 12

MMRM Analysis (mixed model of repeated measures)	**ACP 2 mg (N = 225)**	**Sham (N = 222)**	**Difference**	**% Difference**	**P-Value**
Mean Rate of GA Growth (Slope) (mm) (Square Root Transformation)	0.336	0.392	0.056	14.3%	0.0064[(a)]
Mean Rate of GA Growth (Slope) (mm^2) (Observed)	1.745	2.121	0.376	17.7%	0.0039[(b)]

Explanatory notes - in the above presentation:

(a) Indicates pre-specified primary endpoint analysis; statistically significant;
(b) Indicates descriptive p-value.

We also analyzed the mean change in GA area from baseline to month 12 in GATHER2 using a point analysis, which was the pre-specified primary efficacy endpoint analysis in GATHER1. This analysis was performed based on FAF readings at the same three time points (baseline, month 6, and month 12) as the slope analyses. The results for the 12-month point analysis were consistent with the slope analyses and are described below.

The following tables show the GATHER2 efficacy results for both (A) the mean rate of change in GA area from baseline to month 12 using a point analysis and (B) the mean rate of growth (slope) in GA area over 12 months. These results are provided using both the square root transformation and the observed GA areas.

MMRM Analysis	**ACP 2 mg (N = 225)**	**Sham (N = 222)**	**Difference**	**% Difference**	**P-Value**
Sq. Rt. Transformation					
Mean Change in GA Area (mm)	0.333	0.392	0.059	15.0%	0.0056[(b)]
Mean Rate of GA Growth (Slope) (mm)	0.336	0.392	0.056	14.3%	0.0064[(a)]
Observed Area					
Mean Change in GA Area (mm^2)	1.936	2.341	0.405	17.3%	0.0027[(b)]
Mean Rate of GA Growth (Slope) (mm^2)	1.745	2.121	0.376	17.7%	0.0039[(a)]

Explanatory notes - in the above presentation:

(a) Indicates pre-specified primary endpoint analysis; statistically significant;
(b) Indicates descriptive p-value.

As part of the pre-specified statistical analysis plan for GATHER2, we also analyzed the mean rate of growth (slope) in GA area for ACP 2 mg as compared to sham for pre-specified patient subgroups based on baseline lesion size, baseline visual acuity, baseline autofluorescence pattern, age, and gender. ACP 2 mg showed a reduction in the mean rate of growth (slope) in GA area for all analyzed subgroups.

The pre-specified supportive endpoints in GATHER2 included the mean change in best corrected visual acuity, or BCVA, and the mean change in low luminance best corrected visual acuity, or LL BCVA, from baseline to month 12. For BCVA, a favorable trend for ACP 2 mg was observed, which is consistent with GATHER1. For LL BCVA, a favorable trend was not observed.

Trial Conduct and Patient Retention

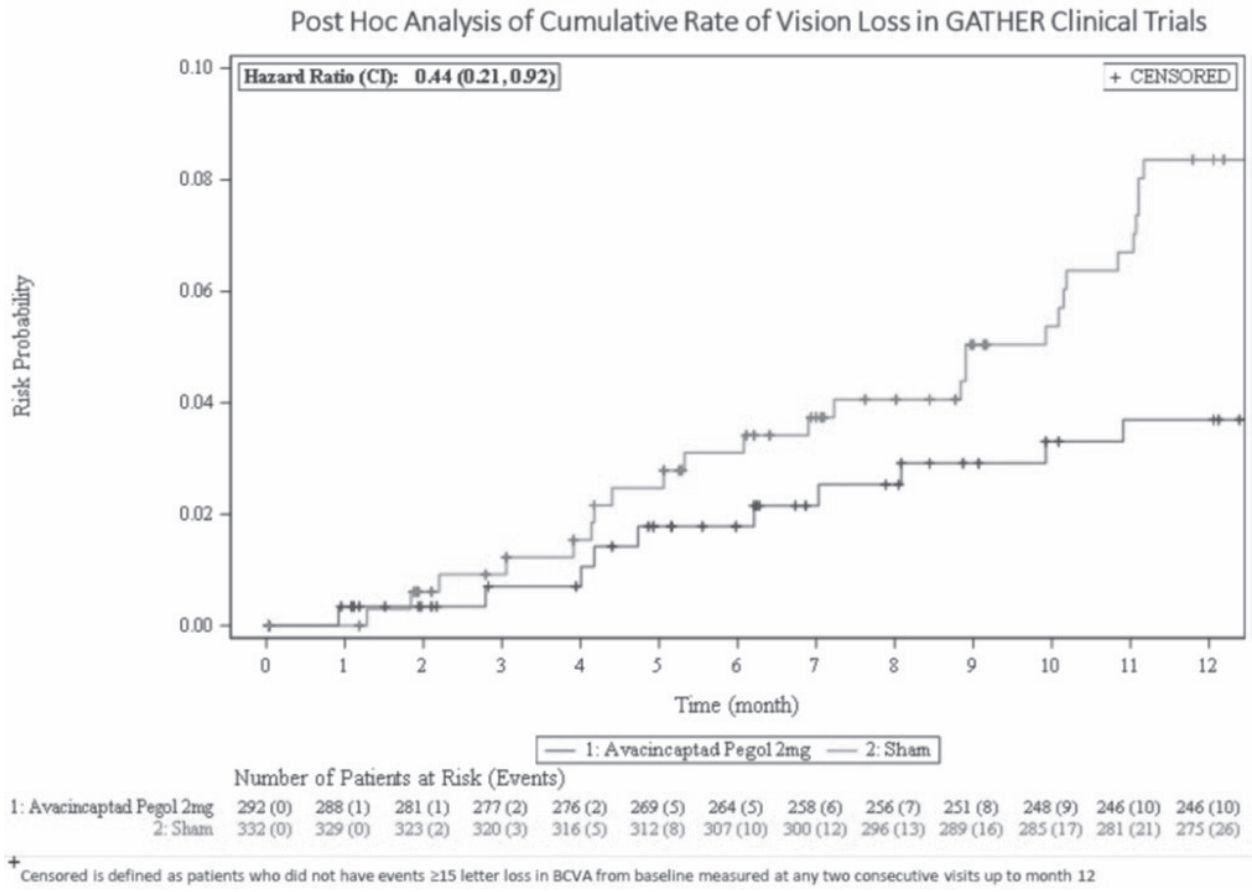
We achieved a 12-month injection fidelity rate for GATHER2 of 92.5%. The 12-month injection fidelity rate for GATHER1 was 87%. The injection fidelity rate is calculated by dividing the total number of actual injections for all patients by the total number of expected injections based on the total number of patients enrolled in the trial. We believe injection fidelity to be the most important and stringent measure of patient retention because it reflects the timely administration of the study drug into the patient's eye.

The number of patients who withdrew or otherwise discontinued from the GATHER2 trial during the first 12 months was 25 (11.1%) in the ACP 2 mg group and 17 (7.7%) in the sham control group. We continue to focus on patient retention and closely monitor the COVID-19 pandemic and its effect on the trial. We remain masked as to the treatment of the patients in the trial.

Post-Hoc Time-to-Event Analysis from GATHER1 and GATHER2

We conducted an exploratory time-to-event analysis from the GATHER1 and GATHER2 clinical trials evaluating reduction in vision loss with ACP 2 mg versus sham treatment. The post-hoc analysis for vision loss from these pivotal trials signals up to a 59% reduction in rate of vision loss with ACP 2 mg compared to sham treatment at 12 months. Vision loss in this analysis was defined as a loss of ≥15 letters (EDTRS) in BCVA from baseline measured at any two consecutive visits up to month 12. This analysis will be presented at the upcoming Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting from April 23-27, 2023.

The results were consistent in the GATHER1 and GATHER2 clinical trials independently, signaling a 44% reduction (Hazard Ratio 0.56 with 95% CI, 0.15-2.06) and a 59% percent reduction (Hazard Ratio 0.41 with 95% CI, 0.17-1.00) respectively in the rate of vision loss with ACP 2 mg compared to sham over the first 12 months of treatment. In a combined analysis of GATHER1 and GATHER2 shown in the accompanying graph, patients treated with ACP 2 mg experienced a 56% reduction (Hazard Ratio 0.44, with 95% CI, 0.21-0.92) in the rate of vision loss compared to sham over the first 12 months of treatment. This post hoc analysis evaluates the potential vision loss signal through 12 months of treatment and is exploratory in nature.



ISEE2009: Open Label Extension Study for Patients Who Completed the GATHER2 Trial

In September 2022, we iniated an open-label extension study, or the OLE study, which is an international, multi-center clinical trial assessing the safety of intravitreal administration of ACP in patients who completed their month 24 visits in the GATHER2 trial. All patients participating in the OLE study will receive monthly doses of ACP 2 mg, regardless of the treatment arm (ACP or sham procedure) that they were randomized to in the GATHER2 trial. The trial will continue until each patient has completed their month 18 study visit or until ACP is commercially available in the relevant jurisdiction.

OPH2001: Completed Phase 1/2a Clinical Trial of ACP 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 ACP 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 ACP over a 36-week treatment period. Patients received an intravitreal injection of ACP at day 0, week 4, week 8, week 24 and week 36 of the trial, with a final follow-up visit at week 48.

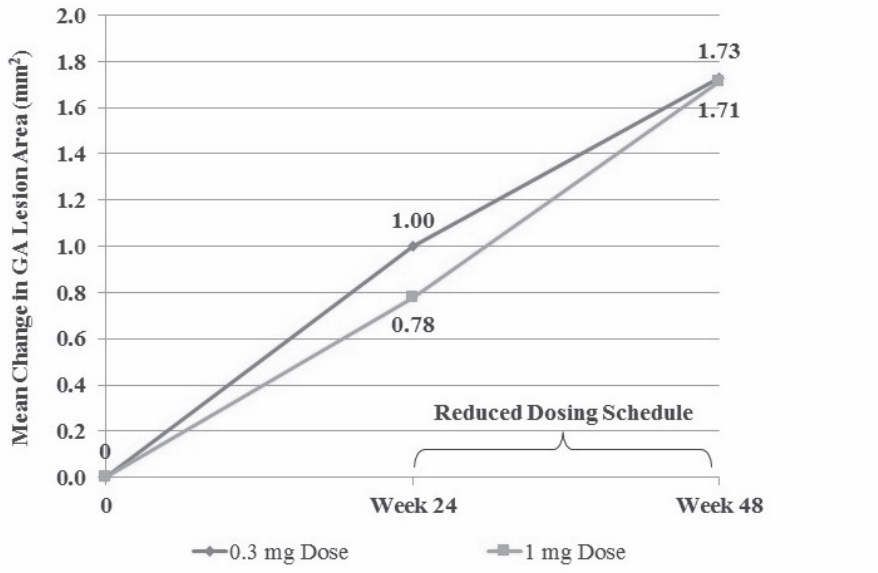
ACP was generally well-tolerated in this trial. We did not observe any evidence of drug related adverse events. We also did not observe any incidence of conversion to wet AMD in eyes treated with ACP. Adverse events were primarily ocular adverse events in the study eye which were related to the injection 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 ACP dose groups, or the efficacy of ACP 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 ACP was dosed more frequently, together with the relative loss of the benefit when ACP was dosed less frequently, may suggest a possible drug effect.

Regulatory Pathway for Marketing Approval of ACP in GA secondary to AMD

To obtain marketing approval of ACP for the treatment of GA secondary to AMD, we expect that we will need favorable results from a total of two independent, adequate and well-controlled pivotal clinical trials, demonstrating the safety and efficacy of ACP in this indication. We believe the results we have obtained from our GATHER1 and GATHER2 trials satisfy this requirement and provide below further explanation for this belief.

FDA Requirements and Status

Based on our interactions with the FDA, we believe it would be sufficient to establish efficacy by showing statistically significant results on the primary efficacy endpoint in the GATHER1 and GATHER2 trials, which is based on measuring GA area growth using FAF. The FDA required analysis for the primary efficacy endpoint is the mean rate of growth (slope) estimated based on GA area measured by FAF over at least three timepoints: baseline, month 6, and month 12. Both GATHER1 and GATHER2 demonstrated a statistically significant reduction in the mean rate of GA area growth (slope) compared to sham when analyzed using the FDA's required analysis.

Based on our interactions with the FDA, we believe it would be sufficient to establish safety by using the safety data collected over 12 months and 18 months from the GATHER1 trial and over 12 months from the GATHER2 trial. We plan to provide additional supportive safety data from our other completed and ongoing trials of ACP in patients with GA, wet AMD, IPCV and STGD1.

We have had a number of interactions with the FDA on our development and regulatory pathway for ACP in GA secondary to AMD, including:

- In July 2021, we obtained a SPA from the FDA for the overall design of GATHER2. Based on the information we submitted, the FDA determined that the design and planned analysis of GATHER2 adequately addressed the objectives necessary to support a future regulatory submission.

- Over 2021 and 2022, we had a number of additional interactions with the FDA on the requirements for and the content of our planned NDA of ACP for the treatment of GA secondary to AMD, which clarified our regulatory pathway in this indication.

- In November 2022, the FDA granted breakthrough therapy designation for ACP for GA secondary to AMD based on the 12-month results from GATHER1 and GATHER2.

- In December 2022, we completed rolling submission of the NDA for ACP for the treatment of GA secondary to AMD, with the clinical and non-clinical portions of the NDA submitted in November 2022 and the chemistry, manufacturing and controls portion of the NDA submitted in December 2022.

In February 2023, the FDA accepted the NDA for filing and granted us priority review with a PDUFA target action date of August 19, 2023. The FDA indicated in their acceptance letter that, as of the time of the FDA acceptance letter, they did not identify any potential review issues and were not currently planning an Advisory Committee meeting for ACP.

EMA and The Medicines and Healthcare Products Regulatory Agency (MHRA) Requirements and Plans

We believe that the safety and efficacy data we have collected to date from the GATHER1 and GATHER2 trials, which are over 18 months and 12 months, respectively, are adequate to support MAA submissions for both the EMA and the MHRA. Our belief is subject to feedback from the EMA and MHRA, with whom we expect to have interactions during the first half of 2023.

We plan to submit MAAs to the EMA and the MHRA for marketing approval of ACP for the treatment of GA secondary to AMD during 2023, following our planned interactions with regulatory authorities in Europe.

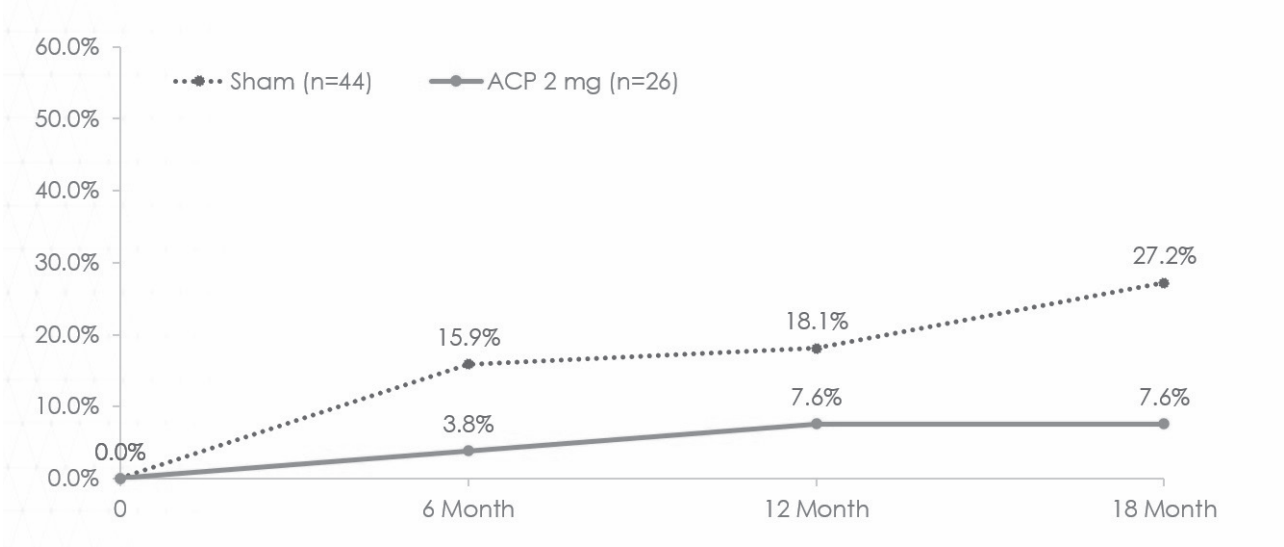
ACP - Potential Pathway in Intermediate AMD

Post-hoc Analyses of GATHER1 Data in Drusen, iRORA and cRORA

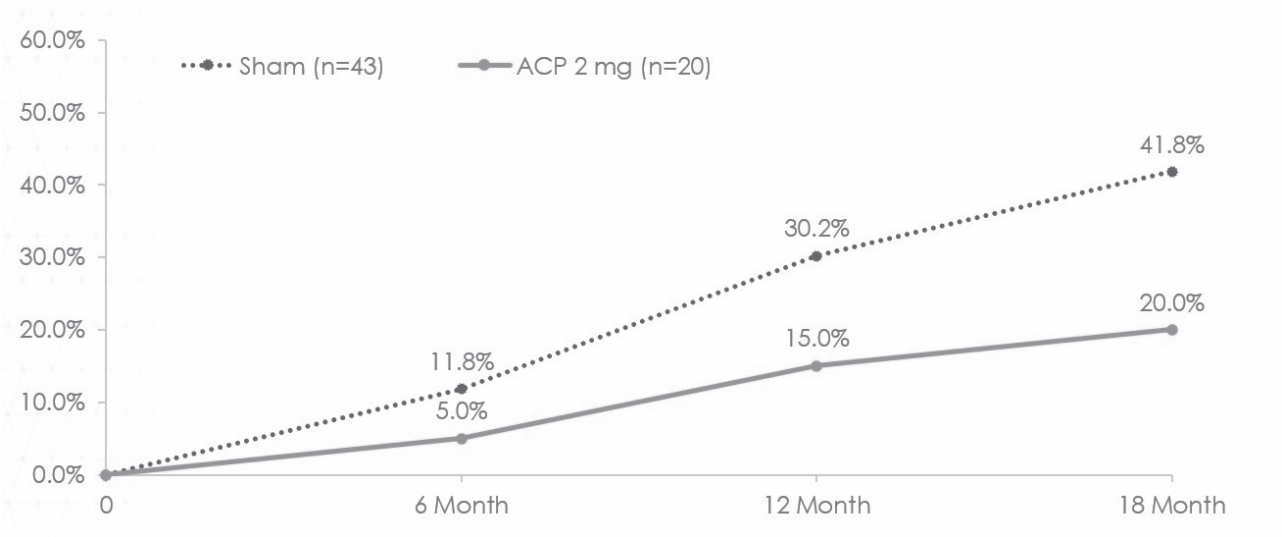
We conducted additional post-hoc analyses on the GATHER1 data, in which we evaluated the progression of iRORA to cRORA, and the progression of drusen to iRORA or cRORA, in patients treated with ACP 2 mg as compared to patients in the corresponding sham group. Drusen, iRORA and cRORA represent progressive stages of AMD.

The post-hoc analysis data show a 19.6% absolute reduction in the rate of progression from drusen to iRORA or cRORA, for the ACP 2 mg group as compared to sham at 18 months, representing a relative reduction of 72%. The data also show a 21.8% absolute reduction in the rate of progression from iRORA to cRORA for the ACP 2 mg group as compared to sham at 18 months, representing a relative reduction of 52%. The following graphs illustrate these results:

Proportion of patients that progress from drusen to iRORA or cRORA (ACP 2 mg compared to sham)



Proportion of patients that progress from iRORA to cRORA (ACP 2 mg compared to sham).



We plan to conduct a similar post-hoc analysis on the GATHER2 data.

Plans in Intermediate AMD

As previously disclosed, we were encouraged by the results of the above post-hoc analyses of the GATHER1 data and were planning to initiate a clinical trial evaluating ACP for the treatment of intermediate AMD, subject to feedback from the FDA and other regulatory authorities. In September 2022, we obtained favorable feedback from the FDA on our development plans. As a result of our interactions with the FDA, we do not believe we need to conduct a new clinical trial of ACP in patients with intermediate AMD. We are continuing further discussions with the FDA on using the GATHER1 and GATHER2 clinical trial data included in the current NDA submission to support treatment of GA associated with earlier stage disease, including in patients with intermediate AMD.

ACP - STGD1 Trials

STAR: Ongoing Phase 2b Clinical Trial of ACP for STGD1

We initially completed patient enrollment for this clinical trial in February 2019 with a total of 95 patients enrolled, none of whom have any remaining study visits. In July 2020, we reopened enrollment in this trial in the United States. We continue to enroll patients and plan to enroll approximately 25 additional patients, with the goal of enrolling a total of approximately 120 patients.

All initially enrolled patients were, and any newly enrolled patients are, randomized in a 1:1 ratio as follows:

- ACP 2 mg, followed by ACP 2mg 14 days later, monthly for three months during an induction phase; followed by ACP 4 mg, administered as two injections of ACP 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 OCT. OCT 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 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 OCT, which shows an OCT image from the perspective of looking at the retina head-on.

We have not previously studied ACP in STGD1 patients and thus do not have any clinical data regarding the effect of ACP in STGD1. We previously engaged the Foundation Fighting Blindness to provide us with data from the Foundation Fighting Blindness'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 STAR trial. 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 ACP in this indication.

Similar to GATHER1, STAR is 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. If the results are positive and statistically significant, we believe this trial could potentially serve as a clinical trial that can support an application for marketing approval. However, we have not yet engaged with the FDA or the EMA about this belief and expectation.

Even though we have reopened patient enrollment, we have been and plan to remain masked to the treatment condition of all patients in the trial. In addition, we have not reviewed and do not plan to review or analyze efficacy data for any patients in the trial, until the 18-month data has been collected and analyzed for all patients enrolled in the trial.

ACP - Wet AMD Trials

OPH2000: Completed Phase 1/2a Clinical Trial of ACP 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 ACP 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 ACP dose levels: 0.03 mg, 0.3 mg, 1 mg, 2 mg and 3 mg. ACP 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 ACP, mild subcapsular cataract in one patient in the group treated with ACP 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 ACP 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 ACP dose groups or the efficacy of ACP 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 ACP 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 ACP for Treatment-Experienced Wet AMD Patients

During the fourth quarter of 2015, we initiated an open-label Phase 2a clinical trial to evaluate ACP'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 ACP development programs, we stopped enrolling patients in this trial as we determined that we would initiate a new ACP 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 ACP for Treatment-Naïve Wet AMD Patients

In 2018, we completed a randomized, dose-ranging, open-label, multi-center Phase 2a clinical trial of ACP in combination with Lucentis 0.5 mg to evaluate the safety of different dosing regimens of ACP in combination with an anti-VEGF agent in treating wet AMD. We enrolled and treated 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, ACP 4 mg two days later and in Group 2, ACP 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 ACP 2 mg on the same day, followed by ACP 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 ACP 2 mg on the same day and in Group 4, ACP 2 mg followed two days later with Lucentis 0.5 mg and ACP 2 mg.

From a safety perspective, ACP 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 ACP 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 ACP dose groups or to evaluate the efficacy of ACP 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.

ACP - IPCV Trials

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

In late 2014, we initiated a very small, uncontrolled, open-label, Phase 2a clinical trial to evaluate ACP'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 ACP for IPCV

In late 2017, we initiated a randomized, dose-ranging, open-label Phase 2a clinical trial of ACP in combination with Eylea in treatment-experienced patients with IPCV. We did not enroll any patients in this clinical trial and decided to

discontinue this clinical trial.

IC-500: HtrA1 Inhibitor Product Candidate

In October 2018, we acquired from funds controlled by Versant Ventures a number of HtrA1 inhibitors. In previous experiments conducted before the acquisition, these HtrA1 inhibitors showed high affinity and specificity for HtrA1 when tested in vitro. In 2020, we selected the lead compound from this group of HtrA1 inhibitors, which we call IC-500, for preclinical development. We are currently developing IC-500 for the treatment of GA and evaluating HtrA1 inhibition as a potential treatment for other stages of AMD and potentially other age-related retinal diseases.

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 GA as well as other stages of AMD and potentially other age-related retinal diseases.

We are continuing the preclinical development of IC-500. We have developed a formulation that we believe will be safe and effective for intravitreal administration into the eye, and are conducting cGMP manufacturing activities for IC-500. We are conducting additional preclinical studies to optimize the dosage, delivery and formulation of IC-500, and planning for IND-enabling toxicology studies to start later in 2023. Based on current timelines and subject to successful preclinical development and cGMP manufacturing, we expect to submit an IND to the FDA for IC-500 during the first half of 2024.

Gene Therapy Research and Development Programs

As we continue to assess our strategic priorities and the market for orphan and age-related retinal diseases and available technologies for addressing those unmet medical needs, we continue to believe in gene therapy as a promising mechanism of action for the treatment of many retinal diseases. We continue to advance our minigene research programs for LCA10, STGD1 and USH2A, respectively. We describe below the December 2022 transaction in which Opus acquired all of our rights, title and interests in and to our assets primarily related to our former gene therapy product candidates IC-100 and IC-200, which we previously developed for rhodopsin-mediated autosomal dominant retinitis pigmentosa and *BEST1*-related IRDs, respectively.

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. 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 shell 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.

Minigene Programs

Starting in 2018, we funded several sponsored research programs at the University of Massachusetts Medical School, or UMMS, seeking to use a minigene approach to develop new gene therapies for several orphan IRDs. These programs (miniCEP290, miniABCA4 and miniUSH2A) are described below. In July 2021, we hired several employees who were previously at UMMS and working on these sponsored research programs, including the principal investigator for these programs. We have transitioned the preclinical research activities for these programs from UMMS to us and have established a laboratory for these employees to continue working on these programs and other preclinical ocular research and development activities.

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 our sponsored research with UMMS was to create and evaluate other *CEP290* minigene constructs in the mouse model and optimize the effect observed in that publication.

We were encouraged by the results of the sponsored research. One of the new minigene constructs shows five times longer duration of functional rescue of the photoreceptors as compared to what was observed in the 2018 publication. 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. UMMS continued experiments to optimize the constructs, which were delayed during 2020 because of restrictions placed by UMMS on animal research activities as a result of the COVID-19 pandemic. We have identified a lead construct from this program and are considering preclinical development options.

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. As part of the sponsored research, UMMS generated and evaluated several *ABCA4* minigene constructs in both *in vitro* and *in vivo* experiments, which yielded what we believe to be encouraging results. We conducted additional experiments to optimize the constructs and assess their efficacy in the mouse model. We have identified a lead construct from this program and are considering preclinical development options.

UMMS granted us an option to obtain an exclusive license to certain patent applications for this program.

miniUSH2A Program for USH2A-Related IRDs

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 nonsyndromic autosomal recessive retinitis pigmentosa. Some of the activities in this program were delayed during 2020 as a result of the closure of UMMS animal research laboratories due to the COVID-19 pandemic. UMMS generated and evaluated several USH2A minigene constructs in *in vitro* experiments and we are planning to evaluate their efficacy in animals. The animal experiments were delayed as a result of transitioning the work from UMMS to us. We are considering our next steps for this research program.

UMMS granted us an option to obtain an exclusive license to certain patent applications for this program.

Opus Asset Purchase Agreement

As part of our previously stated strategy to seek a licensee for IC-100 and IC-200, in December 2022, IVERIC bio Gene Therapy LLC, or the Iveric Subsidiary, our wholly owned subsidiary, entered into an asset purchase agreement with Opus, or the Opus APA, pursuant to which Opus acquired all rights, title and interests in and to Iveric Subsidiary's assets primarily related to IC-100 and IC-200, including Iveric Subsidiary's exclusive license agreements with the University of Florida Research Foundation, Incorporated, or UFRF, and the Trustees of the University of Pennsylvania, or Penn, for both product candidates and certain related sponsored research agreements.

In accordance with the terms of the Opus APA, Iveric Subsidiary received (i) an upfront payment in the amount of $500,000 and (ii) 2,632,720 shares of the Series Seed Preferred Stock of Opus, pursuant to a stock issuance agreement, or the Opus SPA, that the parties entered into currently with the Opus APA, resulting in Iveric Subsidiary's ownership of a high single-digit percentage of the outstanding capital stock of Opus on a fully diluted basis. The Opus APA and the Opus SPA provide for Opus to issue additional shares of capital stock that will maintain Iveric Subsidiary's ownership at a mid to high single-digit percentage of the fully diluted outstanding capital stock of Opus through Opus’s next round of financing in which it raises a specified minimum amount of gross proceeds. Iveric Subsidiary is also eligible to receive (i) contingent development and regulatory milestone payments of up to $12.8 million and (ii) additional sales milestone payments of up to $98.9 million from Opus. Further, Iveric Subsidiary will receive, on a country-by-country and product-by-product basis, an earn-out of a low single-digit percentage on net sales of IC-100 and IC-200.

The Opus APA also contains customary representations, warranties, covenants and indemnification obligations made by Iveric Subsidiary and Opus.

Opus will be responsible for all further research, development, and commercialization of IC-100 and IC-200 globally and replaced Iveric Subsidiary as the exclusive licensee under the license agreements with UFRF and Penn. However, under certain circumstances, Iveric Subsidiary may have certain rights with respect to the potential future commercialization of IC-100 and/or IC-200.

The sale of IC-100 and IC-200 pursuant to the Opus APA closed in December 2022. We have filed the Opus APA and the Opus SPA as exhibits to this Annual Report on Form 10-K, with confidential portions redacted. The foregoing descriptions of the Opus APA and Opus SPA are qualified in their entirety by reference to such agreements as filed.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of ACP, IC-500 or any other product candidate we may develop. We have not yet conducted any process development or manufacturing for our minigene programs. 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.

Manufacturing of pharmaceutical and biological products is a process that involves procurement of starting materials, chemical synthesis or cell culture processing 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 products such as oligonucleotides and 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.

ACP Manufacturing

The process for manufacturing ACP consists of chemical synthesis, purification, pegylation, purification and finally freeze drying to form a powder, which is the active pharmaceutical ingredient, or API. Each of these steps involves relatively common unit operations. In a separate process that follows the freeze drying, the ACP API is dissolved in a liquid solution that includes certain chemicals 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.

We are working with our historical contract manufacturer for ACP drug substance, Agilent Technologies, Inc., or Agilent, to scale up and potentially validate the manufacturing process for ACP drug substance. In 2022, Agilent completed the manufacture of multiple batches of ACP drug substance at a larger scale, a scale which we believe can support potential commercial launch, if approved. We are continuing to work with Agilent on additional scale up and validation activities. In parallel, we are working with a new contract manufacturer with the goal of assessing whether this manufacturer can produce ACP drug substance at an adequate scale for potential commercial use. Subject to successful completion of scale up and validation activities, we currently plan to use Agilent as the primary source of supply of ACP drug substance upon launch, if approved, and the new manufacturer as a second source of supply of ACP drug substance.

We are working with our historical fill/finish manufacturer, Ajinomoto Bio-Pharma Services, or Ajinomoto, on fill/finish of ACP drug product with a new vial, which we believe will allow us to support a more efficient and robust fill/finish operation at a commercial scale. Ajinomoto has produced ACP drug product using the new vial, which we are using for a portion of the second-year study visits for patients in the GATHER2 trial and for the OLE study. We believe Ajinomoto has the capacity to supply us with ACP drug product with the new vial for our expected commercial supply needs upon launch, if approved. We are continuing discussions with Ajinomoto for long-term supply of ACP drug product and are assessing additional suppliers of ACP drug product.

We order the polyethylene glycol, or PEG, starting material used to make ACP drug substance from a sole source third-party manufacturer outside the United States. We currently procure the supply on a purchase order basis and are continuing discussions regarding a long-term supply agreement with this supplier for the PEG starting material. We believe this supplier has the capacity to supply us with the PEG at the scale that we will need for commercial manufacturing.

We have also engaged a manufacturer to package ACP drug product to produce finished goods for potential commercial distribution.

Sustained Release Delivery Technologies for ACP

We are exploring lifecycle management initiatives for ACP with efforts focused on potential sustained release delivery technologies. Our goal is to derive a formulation of ACP with a sustained release delivery technology that reduces the frequency of intravitreal injections that a patient must undergo, while maintaining comparable efficacy and safety to monthly injections. We plan to develop these sustained release delivery technologies for GA and earlier stages of AMD.

One of the technologies that we are evaluating is DelSiTech's proprietary silica-based sustained release technology. We have been encouraged by the results of preliminary feasibility studies of ACP formulated with DelSiTech's silica-based technology and as a result, in June 2022 we entered into a license agreement with DelSiTech, or the DelSiTech License Agreement, under which we obtained a worldwide, exclusive license under specified patent rights and know-how to develop and commercialize new formulations of ACP using DelSiTech's silica-based technology for treating diseases of the human eye.

In addition to DelSiTech's technology, we continue to evaluate other sustained release delivery technologies for ACP. If any of the other resulting formulations are promising, we may pursue long-term development collaborations with those technologies.

IC-500 Manufacturing

The process for manufacturing IC-500 consists of chemical synthesis, purification and spray drying to form a powder, which is the spray dried active pharmaceutical ingredient, or SDAPI. Each of these steps involves relatively common unit operations. In a separate process that follows the spray drying, the IC-500 SDAPI is dispersed in a liquid solution to form a suspension that includes certain pharmaceutical excipients and then is aseptically filled into vials and terminally sterilized. The filled drug product suspension is then diluted to the clinical dose concentration using a diluent. This process of rendering the SDAPI into a liquid suspension and placing it into vials, from which the intravitreal injection is drawn, is referred to as fill/finishing.

We have engaged multiple contract manufacturers to support the various processes necessary for the scale-up and cGMP manufacturing of IC-500 drug substance and drug product for larger scale batches for potential clinical trials. We are continuing preclinical studies to optimize the dosage, delivery and formulation of IC-500.

Human Capital

Our Workforce

As of December 31, 2022, we had 163 full-time employees, compared to 89 full-time employees as of December 31, 2021. These employees support key areas of our business and operations, including commercial planning and operations, medical affairs, clinical development and clinical operations, regulatory affairs and drug safety, data management, scientific research, process and analytical development, drug substance and drug product manufacturing, quality control, materials and supply chain management, and quality assurance, as well as our general and administrative functions and public company infrastructure. We continue to hire strategically to support key areas of our business, including the hiring of a commercial sales force. We expect to complete the hiring of our commercial team of approximately 120 individuals, including a field based sales force of between 50 and 70 representatives, by early April 2023. Diversity is a key factor that we are considering in our hiring of a sales force.

The following are additional data about our full-time employees, as of December 31, 2022:

- 49% of our workforce are women;
- 45% of our workforce are racially diverse (which we define as Asian, African American, Native American and Hispanic);
- 44% of our leadership roles (which we define as Director level and above) are women and 44% of those in leadership roles are racially diverse;
- 31% of our Executive Leadership Team are women; and
- 38% of our Executive Leadership Team are racially diverse.

Throughout 2022, we promoted 12.7% of our workforce into leadership roles. Of these promotions, 47% are women and 43% are racially diverse.

Compensation and Benefits

We believe that our employees are vital to our company's success. To attract and retain talent, we provide competitive compensation and benefits to our workforce, including two medical plans to choose from along with generous Health Reimbursement Account and Health Savings Account offerings. We also offer generous vacation and parental leave. Starting in 2023, we increased the offering periods for our employees to join our Employee Stock Purchase Plan from two to four times per year.

Our turnover rate for 2022 was 6.2%, which is low compared to our peers in our industry.

Culture and People Initiatives

In January 2023, we launched a new corporate narrative to articulate our mission, vision, aspiration and values to reflect our growth and evolution from a development focused organization to a commercial stage organization. We are conducting surveys and focus groups with our employees on our new corporate narrative.

We continue to operate under a hybrid working model (partially remote, partially in office) and expect to continue to do so for the foreseeable near future, with a mix of office-based, field based and laboratory based employees. As we have grown in headcount, we continue to have weekly company meetings to provide business updates and enhance our new employee onboarding programs.

In 2022, we rolled out an employee volunteering and company match program. Based on available information, in 2022, over 25% of our workforce donated funds to or volunteered time for charitable organizations, including for Genspace NYC, a Brooklyn community lab that we sponsor. Our committee for diversity, equity and inclusion, which we established in 2020, continues to find ways to encourage employee volunteering and fundraising for charitable organizations, and bring in outside speakers on topics such as living with disabilities and overcoming unconscious bias.

Sales and Marketing

Our commercial strategy for ACP, as well as for any other product candidate that may be approved, 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, including coverage by payors. For example, we believe more than 90% of GA patients are covered by Medicare Part B, which uses a buy-and-bill reimbursement model for physician administered drugs. As part of our strategy, we will determine whether to retain commercial rights and market and sell the product candidate ourselves or to utilize collaboration, distribution or marketing arrangements with third parties in some or all geographic markets. We expect 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, and the degree and potential degree of acceptance of our product candidate by the relevant physicians in various markets. For example, in the United States, retina specialists perform most of the medical procedures involving diseases of the back of the eye, including intravitreal injections. We believe that retina specialists in the United States are sufficiently concentrated and have experience with the buy-and-bill model such that we could effectively promote an approved buy-and-bill product to these specialists. We also understand that a majority of GA patients in the United States currently are not cared for by retina specialists and instead see general ophthalmologists (GOs) and optometrists (ODs), many of whom are adept at diagnosing GA patients and referring them to retinal specialists for any available treatments. We have factored in these marketplace dynamics in developing our sales and marketing strategy for ACP for GA.

We are continuing to build our commercial capabilities and infrastructure, including our own sales and marketing organization, in anticipation of our potential launch of ACP in the United States for GA, if approved. We are actively hiring qualified personnel across core commercial functions including sales, marketing, patient access and reimbursement, analytics and operations, and product distribution. We expect to complete the hiring for our commercial team by early April 2023, with a total of approximately 120 individuals, including a field based sales force of between 50 and 70 representatives. We believe our field sales force will be capable of covering all of the key retina specialist accounts across the United States by the time of our PDUFA target action date of August 19, 2023.

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.

Based on publicly available information, we are aware of the following competitive products and programs. Other competitive programs may exist of which we are not aware.

Competitive considerations for GA or dry AMD:

- In February 2023, the FDA approved Apellis Pharmaceuticals, Inc., or Apellis's, pegylated, synthetic peptide targeting complement protein C3, pegcetacoplan, for the treatment of GA secondary to AMD. This product has a dosing regimen of once every 25 to 60 days. In December 2022, Apellis submitted an MAA to the EMA. Apellis announced that the EMA had validated their MAA and the application was under review, with a decision expected in early 2024.
- We are aware that LumiThera, Inc. has a medical device using its LT-300 light delivery system, which is approved in the European Union for the treatment of dry AMD. In addition, there are a number of products in preclinical and clinical development by third parties to treat GA or 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 AstraZeneca PLC (which acquired Alexion Pharmaceuticals, Inc. in 2021), Akari Therapeutics, Plc, Annexon Inc., Apellis, Applied Genetic Technologies

Corporation, or AGTC, Biogen Inc., Gemini Therapeutics, Inc. (which merged with Disc Medicine, Inc.), Gyroscope Therapeutics (which was acquired by Novartis AG), IONIS Pharmaceuticals, Inc. (in collaboration with Roche AG), Janssen Pharmaceuticals Inc. (which acquired its program through the acquisition of Hemera Biosciences, LLC), Kanaph Therapeutics Inc, NGM Biopharmaceuticals Inc. and Novartis AG each have complement inhibitors in development for GA or dry AMD, including, in the cases of Gyroscope Therapeutics and Janssen Pharmaceuticals, complement inhibitor gene therapies and in the cases of AGTC and Gemini Therapeutics, research programs on complement factor H gene therapy. We believe that the most advanced of these programs is Apellis's, as described above. Moreover, we are aware that several other companies, including Allegro Ophthalmics, LLC, Alkeus Pharmaceuticals Inc., Astellas Pharma Inc., Aviceda Therapeutics, Boehringer Ingelheim, Lineage Cell Therapeutics, Inc. (which was acquired by Roche AG), Ocugen, Inc., ONL Therapeutics, Inc., Regenerative Patch Technologies, Roche AG, Stealth BioTherapeutics Corp. and Visus Therapeutics, are pursuing development programs for the treatment GA or dry AMD using different mechanisms of action outside of the complement system, including Genentech, Inc. (an affiliate of Roche AG) and Gemini Therapeutics, which are pursuing HtrA1 inhibition as a mechanism of action. We believe that the most advanced HtrA1 inhibitor program in development was Genentech's monoclonal antibody HtrA1 inhibitor, which was being studied in a Phase 2 clinical trial until it was discontinued in October 2022.

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 AGTC, Alkeus Pharmaceuticals, Inc., Beam Therapeutics Inc., Biogen, Generation Bio Co., Kubota Vision Inc. (formerly Acucela), Lin BioScience, Inc., ProQR Therapeutics N.V., or ProQR, and Spark Therapeutics (a subsidiary of Roche AG) each have research or development programs in Stargardt disease. Three of these programs, Alkeus, Kubota and Lin BioScience, are exploring the use of oral therapeutics, while AGTC, Nightstar and Spark are each using a gene therapy approach, Beam is using a base editing approach, and ProQR is using an RNA-based approach. Kubota's product candidate, to which the FDA and the EMA granted orphan drug designation in August 2020, is in Phase 3 development while Alkeus's product candidate is in Phase 2 development. In addition, several academic organizations have early stage programs in Stargardt disease.

Competitive considerations for LCA10:

- We are aware that Editas Medicine, Inc. has a gene editing program for LCA10, for which a Phase 1/2 clinical trial is ongoing, ProQR is developing an RNA-based therapeutic for LCA10 that is currently in Phase 2/3 development, Generation Bio Co. has a preclinical program that utilizes close ended DNA 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 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., Odylia Therapeutics and Wave Life Sciences, Inc. 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. 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 and patent applications covering ACP'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, China, Japan and certain other jurisdictions, and which are expected to expire in 2025, subject to any patent term extensions; and
    - patents and patent applications covering the treatment of certain complement mediated disorders with ACP, ACP for use in a method of treating certain complement mediated disorders or a composition comprising ACP for treating certain complement mediated disorders, which have issued in the United States, the EPO Countries, China, Japan and certain other jurisdictions, and which are expected to expire in 2025, 2026 and 2027, subject to any patent term extensions; and
- patents and patent applications owned by IVERIC bio, Inc.:
    - patents and patent applications covering methods of use for treating GA, Stargardt disease, IPCV and other conditions, and other proprietary technology relating to ACP, which include two issued United States patents with claims covering methods for treating GA with ACP that are expected to expire in 2034, subject to any patent term extensions, and patent applications that are pending in the United States, the EPO Countries, China, Japan and certain other jurisdictions, which, if granted, are expected to expire in 2034, 2038 and 2040, subject to any patent term adjustments or extensions; and
    - patent applications covering methods of using ACP to treat intermediate AMD and other forms of AMD, which are pending under the Patent Cooperation Treaty, or PCT, and which, if granted, are expected to expire in 2041, subject to any patent term adjustments or extensions; and
- patents and patent applications owned by our subsidiary Orion Ophthalmology LLC, or Orion:
    - three families of patents and patent applications covering compositions and methods of use of IC-500 and other HtrA1 inhibitors owned by Orion, some of which are issued patents in the United States or claims that have been allowed by the USPTO, as well as issued patents or allowed claims in other jurisdictions, all of which are expected to expire in 2037, and others are pending in the United States, the EPO Countries, China, Japan and certain other jurisdictions, which, if granted, are expected to expire in 2037, subject to any patent term adjustments or extensions; and
- patent applications in-licensed by Iveric Subsidiary from UMass:
    - two families of 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, China and certain other jurisdictions, and which, if granted, are expected to expire in 2038 and 2040, respectively, subject to any patent term adjustments or extensions.

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. If ACP is approved and we elect a composition of matter patent for patent term extension, we expect to be eligible for up to the full five years of patent term extension in the United States and for a similar length of time under the corresponding mechanism in the EPO Countries.

The expiration dates referred to above are without regard to any patent term adjustments or 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, option 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, including sustained release delivery technologies for ACP, 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 seek collaboration opportunities for our product candidates if we believe the arrangement could assist us in the development or potential commercialization of such product candidate and would otherwise help us pursue our business plan and strategic goals.

ACP - 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 $9.0 million in fees based on our achievement of specified clinical milestone events under the C5 License Agreement, including two milestone payments of $1.0 million and $6.0 million triggered by the positive 12-month data from, and by completion of, the GATHER1 trial, which we paid in March 2020 and October 2020, respectively.

Under the C5 License Agreement, for each anti-C5 aptamer product that we may develop under the agreement, including ACP, we are obligated to make additional payments to Archemix of up to an aggregate of $50.5 million if we achieve specified development, clinical and regulatory milestones, with $24.5 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.

ACP - DelSiTech License Agreement

In June 2022, we entered into the DelSiTech License Agreement with DelSiTech, under which DelSiTech granted us a worldwide, exclusive license under specified patent rights and know-how to develop, have developed, make, have made, use, offer to sell, sell, have sold, otherwise commercialize, export and import ACP using DelSiTech's silica-based sustained release technology for the treatment of diseases of the eye in humans, which we refer to as the Licensed Product. We may grant sublicenses of the licensed patent rights and know-how without DelSiTech's consent.

Diligence Obligations

As a condition to the ongoing effectiveness of DelSiTech's grant of exclusive rights, (a) we would use commercially reasonable efforts to develop the Licensed Product and to seek regulatory approval for the Licensed Product in either the United States or the European Union and (b) we would use commercially reasonable efforts to commercialize the Licensed Product following receipt of regulatory approval in the United States, France, Germany, Italy, Spain or the United Kingdom, as applicable. We have sole discretion as to the use of commercially reasonable efforts for the above, and in the event that we choose not to or fail to use commercially reasonable efforts to develop or commercialize the Licensed Product, DelSiTech's sole remedy for such failure is to convert the licenses granted to us under the DelSiTech License Agreement from exclusive to non-exclusive.

Financial Terms

In June 2022, we paid DelSiTech a €1.25 million upfront license fee, which we have recognized as a research and development expense. We further agreed to pay DelSiTech up to an aggregate of €35.0 million if we achieve specified clinical and development milestones with respect to the Licensed Product. In addition, we agreed to pay DelSiTech up to an aggregate of €60.0 million if we achieve specified commercial sales milestones with respect to worldwide net sales of the Licensed Product.

We are also obligated to pay DelSiTech royalties at a low single-digit percentage of net sales of the Licensed Product. The royalties payable by us are subject to reduction under specified circumstances. Our obligation to pay royalties under the DelSiTech License Agreement will continue on a country-by-country basis until the later of: (a) the expiration of the last-to-expire licensed patent rights covering the Licensed Product in the country of sale, or (b) expiration of all regulatory exclusivity for the Licensed Product in the country of sale.

Term and Termination

The DelSiTech License Agreement also contains representations and warranties, covenants, indemnification and other negotiated provisions, including confidentiality obligations, customary for transactions of this nature. Unless earlier terminated by us or DelSiTech, the DelSiTech License Agreement will expire on a country-by-country basis upon the expiration of our obligation to pay royalties to DelSiTech on net sales of the Licensed Product. Upon expiration of the DelSiTech License Agreement, the licenses granted by DelSiTech to us will become fully paid up and irrevocable. We may terminate the DelSiTech License Agreement at any time for any reason upon 60 days' prior written notice to DelSiTech. Either party may also terminate the DelSiTech License Agreement if the other party materially breaches the DelSiTech License Agreement and does not cure such breach within a specified cure period.

Following any termination of the DelSiTech License Agreement prior to expiration of the term of the DelSiTech License Agreement, all rights to the licensed patent rights and know-how that DelSiTech granted to us will revert to DelSiTech, subject to our right to sell off any Licensed Product in our inventory as of the effectiveness of such termination.

IC-500 - Inception 4 Merger Agreement

In October 2018, we acquired IC-500 and a number of other HtrA1 inhibitors through our acquisition of Inception 4, Inc., or Inception 4, which was previously a privately held biotechnology company controlled by funds owned by Versant Ventures. 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. Following the Inception 4 Merger, Inception 4 was merged into our wholly-owned subsidiary Orion, which currently owns the rights to IC-500 and the other HtrA1 inhibitors acquired in the Inception 4 Merger.

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 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. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor.

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. A sponsor 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;
- design of a clinical trial protocol and 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 a sponsor 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. These studies are typically referred to as IND-enabling studies. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations and the United States Department of Agriculture's Animal Welfare Act, if applicable.

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, sponsors 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 or ethics committee 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.

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, 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.

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Moreover, a pivotal trial is a clinical trial that is believed to satisfy FDA requirements for the evaluation of a product candidate's safety and efficacy such that it can be used, alone or with other pivotal or non-pivotal trials, to support regulatory approval. Generally, pivotal trials are Phase 3 trials, but they may be Phase 2 trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In December 2022, with the passage of Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, actions plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

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.

Finally, sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health, or NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Both NIH and the FDA have recently signaled the government's willingness to begin enforcing those requirements against non-compliant clinical trial sponsors. The failure to submit clinical trial information to clinicaltrials.gov, as required, is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. Although the FDA has historically not enforced these reporting requirements due to HHS's long delay in issuing final implementing regulations, those regulations have now been issued and the FDA has issued several Notices of Noncompliance to manufacturers since April 2021.

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. In April 2020, we adopted an expanded access policy, which is available on our website in accordance with the 21st Century Cures Act.

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.

Manufacturing and Other Regulatory Requirements

Concurrent with clinical trials, sponsors usually complete additional animal safety studies, develop additional information about the chemistry and physical characteristics of the product candidate and finalize a process for manufacturing commercial quantities of the product candidate in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other criteria, the sponsor must develop methods for testing the identity, strength, quality, and purity of the finished product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo

unacceptable deterioration over its shelf life.

Specifically, the FDA's regulations require that pharmaceutical products be manufactured in specific approved facilities and in accordance with cGMPs. The cGMP regulations include requirements relating to organization of personnel, buildings and facilities, equipment, control of components and product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports and returned or salvaged products. Manufacturers and other entities involved in the manufacture and distribution of approved pharmaceuticals are required to register their establishments with the FDA and some state agencies, and they are subject to periodic unannounced inspections by the FDA for compliance with cGMPs and other requirements. Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. The FDA's regulations also require, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the sponsor and any third-party manufacturers involved in producing the approved product.

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.

The FDA has issued various guidance documents regarding gene therapies, including 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. We expect the FDA to issue additional guidance on gene therapies.

Special Protocol Assessment Agreements

A Special Protocol Assessment, or SPA, agreement is an agreement between a drug manufacturer and the FDA on the design and size of studies and clinical trials that can be used for approval of a drug or biological product. The FDA's guidance on such agreements states that an agreement may not be changed by the manufacturer or the agency unless through a written agreement of the two entities or if FDA determines a substantial scientific issue essential to determining the safety or effectiveness of the drug. The protocols that are eligible for SPA agreements are: animal carcinogenicity protocols, final product stability protocols and clinical protocols for Phase 3 trials whose data will form the primary basis for an efficacy claim.

The FDA may meet with sponsors, provided certain conditions are met, for the purpose of reaching an SPA agreement on the design and size of clinical trials intended to form the primary basis of an efficacy claim in a marketing application. If a sponsor makes a reasonable written request to meet with the FDA for the purpose of reaching agreement on the design and size of a clinical trial, then the FDA will meet with the sponsor. If an agreement is reached, the FDA will reduce the agreement to writing and make it part of the administrative record. An agreement may not be changed by the sponsor or FDA after the trial begins, except with the written agreement of the sponsor and FDA, or if the director of the FDA reviewing division determines that "a substantial scientific issue essential to determining the safety or effectiveness of the drug" was identified after the testing began. If a sponsor and the FDA meet regarding the design and size of a clinical trial and the parties cannot agree that the trial design is adequate to meet the goals of the sponsor, the FDA will clearly state the reasons for the disagreement in a letter to the sponsor.

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 sponsors 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 2023 is $3,242,026 for an application requiring clinical data. The sponsor of an approved application is also subject to an annual program fee, which for fiscal year 2023 is $393,933. 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 within 60 calendar days of its receipt and must inform the sponsor by that time or before whether the application is sufficiently complete to permit substantive review. In the event that FDA determines that an application does not satisfy this standard, it will issue a Refuse to File, or RTF, determination to the sponsor. The FDA may request additional information rather than accept an application for filing. 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 target action date may be extended by the FDA for three additional months to consider new information or clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission.

In connection with its review of 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 and the integrity of the clinical data submitted. With passage of FDORA, Congress clarified the FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to the FDA as well as other persons holding study records or involved in the study process.

In addition, as a condition of approval, the FDA may require a sponsor 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

The FDA reviews an application to determine, among other things, whether the product is safe and whether it is effective for its intended use(s), with the latter determination being made on the basis of substantial evidence. The FDA has interpreted this evidentiary standard to require at least two adequate and well-controlled clinical investigations to establish

effectiveness of a new product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard.

After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA will issue either a Complete Response Letter, or CRL, or an approval letter. To reach this determination, the FDA must determine that the expected benefits of the proposed product outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and efficacy in the NDA or potency, purity and safety in a BLA.

A CRL 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 a CRL is issued, the sponsor will have one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six month extension to respond.

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. None of these expedited programs changes the standards for approval, but each may help expedite the development or approval process governing product candidates.

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. In April 2020, the FDA granted fast track designation to ACP for the treatment of GA secondary to dry AMD.

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. In November 2022, the FDA granted breakthrough therapy designation to ACP for GA secondary to AMD.

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. In February 2023, the FDA granted priority review to our NDA for marketing approval of ACP for the treatment of GA secondary to AMD.

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.

The FDA may award priority review vouchers, or PRVs, 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 PRV, which the sponsor may redeem to receive priority review of a subsequent marketing application for a different product. In lieu of using the PRV for one of its own product candidates, a sponsor may sell that voucher for use by a third party. Current prices for these PRVs range in the hundreds of millions of dollars. The current rare pediatric disease priority review voucher program will expire on September 30, 2024, although a drug designated as a rare pediatric disease treatment by September 30, 2024, can still receive a priority review voucher but no later than September 30, 2026.

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 spend 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, manufacturers are prohibited from soliciting, encouraging or promoting unapproved uses of a product. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Moreover, with passage of the Pre-Approval Information Exchange Act in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance but the new legislation explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products.

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, a sponsor must submit an abbreviated new drug application, or ANDA, to the FDA. An ANDA sponsor 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 sponsor 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.

The FDA is also authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the sponsor to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the sponsor for approval of the application "were not conducted by or for the sponsor and for which the sponsor has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Sponsors of RLDs are required to list in the FDA's Orange Book each patent with claims covering the RLD or approved methods of using the RLD. An ANDA sponsor 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 sponsor 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 sponsor.

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 sponsor 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. This interpretation was confirmed with enactment of the Ensuring Innovation Act in April 2021. We expect ACP to be eligible for the five-year period of data exclusivity, if approved. 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 sponsor, 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, a sponsor 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." To date, the FDA has approved a number of biosimilars and the first interchangeable biosimilar product was approved on July 30, 2021, and a second product previously approved as a biosimilar was designated as interchangeable in October 2021. The FDA has also issued numerous guidance documents outlining its approach reviewing and licensing biosimilars and interchangeable biosimilars under the PHSA.

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, there have been recent government proposals to reduce the 12-year reference product exclusivity period, but none has been enacted to date. At the same time, many states have passed laws or amendments to laws, including laws governing pharmacy practices, which are state-regulated, involving 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 target action 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 September 2021, the FDA issued final guidance describing its current thinking on when a gene therapy product is the "same" as another product for purposes of orphan exclusivity. Under the guidance, if either the transgene or vector differs between two gene therapy products in a manner that does not reflect "minor"

differences, the two products would be considered different drugs for orphan drug exclusivity purposes. The FDA indicated that it will determine whether two vectors from the same viral class are the same on a case-by-case basis and may consider additional key features in assessing sameness. 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. In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

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 regulatory exclusivity. For drug products, the six month exclusivity may be attached to the term of any existing patent or regulatory exclusivity, including orphan drug exclusivity and regulatory exclusivities available under the Hatch-Waxman provisions of the FDCA. For biologic products, the six month period may be attached to any existing regulatory exclusivities but not to any patent terms. 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) sponsor 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 the United Kingdom or 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

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014 became effective in the European Union and replaced the prior Clinical Trials Directive 2001/20/EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency 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 Member State of the European Union, or EU Member State, will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the EMA and available to clinical trial sponsors, competent authorities of the EU Member States and the public.

Beyond streamlining the process, the new Regulation includes a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors, and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed

by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of 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 sponsor may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the EU at the EudraCT website.

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 a sponsor 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, a sponsor 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.

PRIME Designation

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other

development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated agency contact and rapporteur from the CHMP or Committee for Advanced Therapies are appointed early in the PRIME scheme, facilitating increased understanding of the product at EMA's Committee level.

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. We expect ACP to be eligible for the eight years of data exclusivity and two additional years of market exclusivity, if approved. Data exclusivity prevents sponsors 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 sponsor 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. The market exclusivity period can be extended by two years following completion of an agreed upon pediatric investigation plan. 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, sponsors 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 sponsor actually complied with the agreed studies and measures listed in each relevant PIP. If a sponsor 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 or alternatively a one year extension of the regulatory market exclusivity from ten to eleven years, as selected by the marketing authorization holder.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom's withdrawal from the EU took place on January 31, 2020. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law whereas Northern Ireland continues to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the U.K. the body of EU law governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the EU.

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. Efforts to control drug pricing have garnered bipartisan support in the U.S. Congress. Under both the previous Trump Administration and the current Biden Administration, various U.S. government agencies, including the FDA and the Center for Medicare & Medicaid Services, or CMS, proposed a number of rules intended to curb drug prices. For example, in October 2020, the Department of Health and Human Services, or HHS, and the FDA published a final rule

allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA.

Further, on July 9, 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The executive order directs HHS to create a plan within 45 days to combat "excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging." On September 9, 2021, HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to: (a) make pharmaceutical prices more affordable and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; (b) improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year. At the state level, individual states are increasingly aggressive in 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. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers, and wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional healthcare organizations 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 healthcare programs. These measures could reduce the ultimate demand for our products, if and once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

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. Over the past decade, 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, or BCA, led to aggregate reductions in Medicare payments to providers of up to 2% per fiscal year from 2013 through 2031, 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. We expect that ACP, if approved for GA, would be reimbursed by the Medicare Part B "buy and bill" reimbursement model, under which physicians purchase ACP from us or a wholesaler/distributor, and then bill Medicare for their costs following administration. Medicare Part B currently provides for reimbursement to the physicians at a rate equal to the average sales price for the product plus a six percent markup. The BCA has reduced the effective rate of that markup to 4.3%. Any further 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, since passage of the ACA, there have been several lawsuits challenging the ACA, and we expect additional lawsuits may be filed.

Despite those developments, we expect the 117th Congress and the Biden Administration to support and expand on the ACA. For example, on January 28, 2021, President Biden issued an executive order directing federal agencies to review all existing regulations, policies and a variety of other guidance that limit Americans' access to high-quality healthcare and to consider actions that will protect and strengthen Medicaid, the ACA and, more generally, access to affordable healthcare for Americans. Under this order, federal agencies are to advance President Biden's overall access policy and make determinations as to whether additional actions are necessary. Specifically, the agencies must examine, among other things, policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19, and policies that undermine the health insurance marketplace or other markets for health insurance.

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, other healthcare providers 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, state pharmaceutical sales representative listing requirements and other consumer protection 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, and require the notification of any breaches 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.

Our Corporate Information

Our principal executive offices are located at 8 Sylvan Way, Parsippany, New Jersey, 07054, and our telephone number is (609) 474-6755. 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 is highly dependent on the success and potential commercialization of ACP and our other 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 dependent on the progress of our research and development programs, including our ongoing and any future clinical trials for ACP, our preclinical development program for IC-500, and our gene therapy research programs. In particular, we are highly dependent on the success of ACP, and any delays or issues with its potential marketing approval or its potential commercialization will likely cause the value of your investment to decline significantly. 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 or other factors, with the possible result that none of our product candidates or other programs result in the development of marketable products. Although we have results from two large-scale, pivotal clinical trials (GATHER1 and GATHER2) with safety and efficacy data that we believe are sufficient to seek and obtain marketing approval for ACP for GA secondary to AMD, we need to complete activities necessary to obtain marketing approval, including the qualification of one or more commercial manufacturers through pre-approval inspections with regulatory authorities. We are working to transition from a company having a product development focus to a company capable of commercializing pharmaceutical products. At this time, we are continuing to hire commercialization personnel and build a commercial infrastructure for the potential commercialization of ACP, if approved. We may not be successful in such a transition, as our company has never conducted the sales, marketing, manufacturing 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.

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;
- 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, validating and receiving regulatory approval of our manufacturing processes and our third-party manufacturers' facilities and ensuring adequate supply of drug substance, 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 Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, or FDCA, or the Orphan Drug Act 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 Good Laboratory Practices, or GLP, 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.

We have a history of significant operating losses. We expect to continue to incur losses until such time, if ever, that we successfully commercialize one or more of 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 common stock and 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, our follow-on public offerings, which we closed in February 2014, December 2019, June 2020, July 2021, October 2021 and December 2022 and borrowings under the 2022 Term Loan Facility, pursuant to the Loan Agreement with Hercules and SVB. As of December 31, 2022, we had an accumulated deficit of $864.8 million. Our net loss was $185.2 million for the twelve months ended December 31, 2022, and we expect to continue to incur significant operating losses for the foreseeable future.

ACP is in clinical development, IC-500 is in preclinical development, and we are exploring multiple sustained release delivery technologies for ACP and advancing multiple gene therapy research programs. We expect our research and development expenses to increase as we pursue these programs as currently planned. We could incur additional research and development expenses if we modify or further expand the scope of our clinical trials, such as our initiation of the OLE study for ACP in GA secondary to AMD, our preclinical development programs or our gene therapy research programs, or if we in-license or acquire, and undertake development of, additional product candidates and technologies, including additional sustained release delivery technologies for ACP and any promising product candidates that emerge from our gene therapy research programs. We could also incur additional research and development expenses if, for example, we are required by the

FDA, the EMA or regulatory authorities in other jurisdictions, or if we otherwise decide, to perform clinical trials and/or nonclinical or other studies in addition to those we currently expect to conduct. If we experience delays or disruptions to our research and development programs, including delays in patient enrollment or issues with patient retention or patients missing scheduled visits and treatments, if we experience issues with our preclinical development programs, such as unfavorable toxicology or other preclinical data, if we experience issues with the manufacture and supply of product candidates, including issues with process development or manufacturing scale-up activities, whether such delays or disruptions are due to the COVID-19 pandemic or other reasons, we could incur additional and unexpected expenses as a result of such delays or disruptions and our business and financial results may be materially impacted. Furthermore, if we successfully develop and expect to 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 have started incurring these expenses as we prepare for the potential commercialization of ACP. We are party to agreements with Archemix with respect to ACP, DelSiTech with respect to formulations of ACP with DelSiTech's silica-based sustained release delivery technology, the former equityholders of Inception 4 with respect to IC-500, and UMass with respect to any potential product candidates from our miniCEP290 program, in each case, that impose significant milestone payment obligations on us if we or a potential collaborator achieves specified clinical, regulatory and commercial milestones with respect to these product candidates, as well as certain royalties on net sales with respect to formulations of ACP with DelSiTech's silica-based sustained release delivery technology 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:

- build our commercial operations and sales, marketing and distribution capabilities for ACP;
- expand our outsourced manufacturing capabilities for ACP and IC-500;
- continue the development of ACP in GA, STGD1 and potentially other indications;
- seek marketing approval for ACP and any other product candidates that successfully complete clinical trials;
- in-license or acquire the rights to, and pursue the development of, other product candidates or technologies for retinal diseases, such as sustained release delivery technologies for ACP;
- continue the development of IC-500 and pursue our gene therapy research programs;
- maintain, expand and protect our intellectual property portfolio;
- hire additional commercial, medical affairs, clinical, regulatory, pharmacovigilance, manufacturing, quality control, quality assurance and scientific personnel; 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 revenues 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.

Although we believe we have sufficient cash resources to launch ACP for GA secondary to AMD in the United States, if approved based on our expectations, we may require additional funding beyond what we currently expect or sooner than we currently expect. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate one or more of our product development programs or commercialization efforts.

As of December 31, 2022, we had approximately $646.8 million in cash, cash equivalents and available-for-sale securities. We estimate that our cash, cash equivalents, available for sale securities and committed loan facilities will be sufficient to fund our planned capital expenditure requirements, debt service obligations and operating expenses through at least the next twelve months. These estimates do not include any potential new borrowings under the 2022 Term Loan Facility with Hercules and SVB beyond the $25.0 million that we plan to borrow during 2023 based on our achievement of the performance milestone related to the FDA's acceptance of our NDA for filing.

Although we believe we have sufficient financial resources to launch ACP for GA secondary to AMD in the United States, if approved based on our expectations, we may need additional funding to continue to commercialize ACP for GA, if approved. We expect we will require substantial, additional funding in order to complete the activities necessary to develop and commercialize ACP for other indications, a sustained release delivery technology for ACP or any of our other product candidates. 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 ACP for any other indication, a sustained release delivery technology for ACP or for any of our other product candidates.

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

- the costs, timing and outcome of regulatory filings and reviews of our product candidates, including regulatory review of our filed NDA and the planned submission of MAAs for ACP in GA secondary to AMD;
- the timing, scope and costs of establishing a commercial infrastructure for potential commercialization of ACP, including the hiring and deployment of a sales force and the establishment of sales, marketing and distribution capabilities;
- the scope, progress, costs and results of process development, manufacturing scale-up and validation activities, analytical method development and qualification, and stability studies associated with ACP and our other product candidates;
- the scope, progress, costs and results of our current and future ACP clinical programs and any further development we may undertake;
- our ability to establish collaborations on favorable terms, if at all, if we choose to do so, including a potential collaboration for the further development and potential commercialization of ACP in one or more territories outside the United States;
- the extent to which we in-license or acquire rights to, and undertake research or development of, additional product candidates or technologies, including sustained release delivery technologies for ACP;
- the extent of our debt service obligations and our ability, if desired, to refinance any of our existing debt on terms that are more favorable to us;
- the scope, progress, costs and results of our efforts to develop IC-500, including activities to establish manufacturing capabilities and other preclinical development activities to enable us to submit an IND for this product candidate;
- the scope, progress, costs and results from our gene therapy 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 timing and extent of delays or disruptions to our research and development programs as a result of the COVID-19 pandemic and other macro-economic events;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending intellectual property-related claims; 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.

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. For example, the COVID-19 pandemic and other macro-economic events, such as the current high levels of inflation, and governmental responses to those events have caused volatility and uncertainty in the financial markets as well as additional volatility in the price of our stock, which may result in prospective investors being less likely to invest new capital. 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 successful in raising approximately $324.3 million in net proceeds in an underwritten public offering of our common stock in December 2022, 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, Nasdaq listing rules 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 or reduce our future commercialization efforts, or delay, reduce or terminate the development of one or more of our product candidates.

We may require additional funding beyond what we currently expect due to unforeseen or other reasons. Our costs may exceed our expectations if the timeline for potential commercial launch of ACP is accelerated, if we need to establish commercial infrastructure or capabilities, including hiring additional personnel or conducting additional disease-state awareness activities, to a greater extent than we have planned, or if we choose not to or are unable to find a collaborator for commercialization of ACP in one or more territories outside the United States. Our costs may also exceed our expectations if we experience an issue with manufacturing, such as issues with process development, scale-up and validation, or establishing and qualifying second source suppliers and ensuring adequate inventory for our expected needs, including potential launch of ACP; if we experience an issue in our clinical trials, such as issues with patient enrollment, the retention of enrolled patients, enrolled patients maintaining scheduled visits and receiving scheduled treatments, or the availability of drug supply; if we experience an issue in our preclinical development programs, such as unfavorable toxicology or other preclinical data; or if we modify or further expand the scope of our clinical trials, preclinical development programs or gene therapy 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 trials or nonclinical or other studies in addition to those we currently expect to conduct. For example, we believe that the data from the GATHER2 trial, together with other available data, are sufficient to support applications for marketing approval in the United States, the European Union and the United Kingdom. We may subsequently decide to, or be required by regulatory authorities to, conduct additional clinical trials or nonclinical studies of ACP in order to seek or maintain marketing approval or qualify for reimbursement approval. In addition, the COVID-19 pandemic and other macroeconomic events may result in disruptions to the progress of the GATHER2 or STAR trials or the OLE study, including slowing patient enrollment in STAR or causing enrolled patients in either trial to miss their scheduled visits or drop out in greater numbers than we expect, or disruptions to our other research and development programs, which could cause us to continue to expend our cash resources while not progressing our research and development programs as expeditiously as we would have had the pandemic not occurred or persisted. 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 obtain regulatory approval and launch ACP in GA secondary to AMD. Our future commercial revenues, if any, will be derived from product sales, which may not be available or become substantial for a period of time following launch. In addition, if approved, our products 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. For example, in July 2022, we entered into the Loan Agreement with Hercules and SVB, providing for the 2022 Term Loan Facility, pursuant to which we have total borrowing capacity under several tranches of up to $250.0 million in aggregate principal amount, of which (i) $50.0 million was drawn in July 2022 upon execution of the Loan Agreement and an additional $50.0 million was drawn in December 2022 after our achievement of a specified performance milestone relating to the GATHER2 trial data we obtained for ACP in September 2022, (ii) an additional tranche of $25.0 million is available to be drawn at our option anytime through September 30, 2023 which we plan to draw in 2023, (iii) an

additional tranche of $75.0 million may be drawn at our option at any time after our achievement of a specified performance milestone relating to the approval of the NDA by the FDA through the earlier of 90 days after achievement or September 30, 2024 and (iv) an additional $50.0 million is available subject to approval of the lenders' investment committee in its discretion. However, if we do not satisfy the remaining specified performance milestone or the lenders do not otherwise approve additional borrowings, we will not have access to the remaining amounts of the 2022 Term Loan Facility. 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, would involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, declaring dividends, making certain investments or entering into certain other transactions. For example, the covenants under the Loan Agreement include limitations on our ability to obtain additional financing, to make certain investments and to enter into certain other transactions.

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 agreement and plan of merger pursuant to which we acquired IC-500, or the Inception 4 Merger Agreement, 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 UMass as partial upfront consideration for the in-license of our miniCEP290 program, and are obligated to issue up to 75,000 additional shares to UMass upon the achievement of a development milestone.

In March 2021, we filed a shelf registration statement on Form S-3, or the March 2021 Shelf Registration, pursuant to which we may offer and sell shares of common stock, debt securities and other securities for aggregate gross sale proceeds of up to $300.0 million, of which we may offer and sell up to $100.0 million from time to time pursuant to an "at-the-market" sales agreement, or the ATM Agreement, we entered into in March 2021 with Cowen and Company, LLC, or Cowen, as agent, subject to the terms and conditions described in the ATM Agreement and SEC rules and regulations. In July 2021, we issued and sold 13,397,500 shares of our common stock in an underwritten public offering under the March 2021 Shelf Registration. We have not yet issued and sold any shares of common stock under our "at-the-market" offering program. In addition, in October 2021, we filed an automatically effective shelf registration statement, or the October 2021 Shelf Registration, under which we may issue an indeterminate amount of shares of common stock, debt securities and other securities. In October 2021 and December 2022, we issued and sold 10,350,000 shares of our common stock and 15,352,500 shares of our common stock, respectively, in two underwritten public offerings under the October 2021 Shelf Registration. If we make further sales under the March 2021 Shelf Registration or the October 2021 Shelf Registration or 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, royalty transactions, 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 operating activities may be restricted as a result of covenants related to the outstanding indebtedness under our Loan Agreement with Hercules and SVB and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.

As more fully described in "Management's Discussion and Analysis of Financial Condition and Results of Operations —Contractual Obligations and Commitments", in July 2022, we entered into the 2022 Term Loan Facility. The 2022 Term Loan Facility is secured by a lien on substantially all of our assets, including intellectual property, with certain limited exceptions set forth in the Loan Agreement. The Loan Agreement contains various covenants that limit our ability to engage in specified types of transactions. These covenants limit our ability to, among other things, sell, transfer, lease or dispose of certain

assets; incur indebtedness; encumber or permit liens on certain assets; make certain investments and acquisitions; make certain restricted payments, including paying dividends on, or repurchasing or making distributions with respect to, our common stock; and enter into certain transactions. Our business may be adversely affected by these restrictions on our ability to operate our business.

The covenants under the 2022 Term Loan Facility also include a requirement to maintain, during the period commencing on May 15, 2023, and ending on August 14, 2024, certain minimum levels of cash in accounts subject to a control agreement in favor of Hercules as agent, which we refer to as Qualified Cash.

Further, starting on August 15, 2024, we will be required to maintain a certain minimum amount of trailing six-month net product revenue from sales of ACP, tested on a quarterly basis. However, this revenue covenant will be waived during periods in which we (x) (i) maintain a market capitalization in excess of $600.0 million and (ii) maintain Qualified Cash in an amount greater than or equal to fifty percent (50%) of the outstanding term loan advances made under the 2022 Term Loan Facility at such time or (y) maintain Qualified Cash in an amount greater than or equal to ninety percent (90%) of the outstanding term loan advances made under the 2022 Term Loan Facility at such time.

A breach of any of the covenants under the Loan Agreement could result in a default under the 2022 Term Loan Facility. If an event of default under the 2022 Term Loan Facility occurs, including a material adverse effect, subject to certain exceptions, on our business, operations, properties, assets or financial condition, the lenders could elect to declare all amounts outstanding, if any, to be immediately due and payable and terminate all commitments to extend further credit. If there are any amounts outstanding that we are unable to repay, the lenders could proceed against the collateral granted to them to secure such indebtedness.

In addition, our outstanding debt combined with our other financial obligations and contractual commitments, could have significant adverse consequences, including:

- requiring us to dedicate a substantial portion of cash, cash equivalents and available for sale securities to the payment of interest on, and principal of, our debt, which would reduce the amounts available to fund working capital, commercialization expenditures, product development efforts and other general corporate purposes;
- limiting our flexibility in planning for, or reacting to, changes in our business and our industry; and
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

We intend to satisfy our current and future debt service obligations with our existing cash, cash equivalents and available for sale securities, potential future product revenues and funds from external sources. However, we may not have sufficient funds or may be unable to arrange for additional financing to pay the amounts due under the 2022 Term Loan Facility. Funds from external sources may not be available on acceptable terms, if at all.

The COVID-19 pandemic, which is a fluid situation, has adversely affected and may continue to negatively affect our business and operations in a number of ways, and its long-term effects are uncertain. In addition, the pandemic and other macroeconomic events have caused substantial disruptions in the financial markets and economies, which could adversely affect our business and operations.

Since March 2020, the COVID-19 pandemic and measures taken to contain it have affected our business and operations in a number of ways. These include, but are not limited to, the following:

- Clinical Trial Operations. The pandemic has affected how we conduct our clinical trials, including patient recruitment and efforts to support patient visits to our clinical trial sites. Although the pandemic did not materially affect our clinical trials in 2022, we do not know if and how the pandemic may affect the continued progress of our ongoing clinical trials or any future clinical trials we may conduct. For a more detailed discussion of the impact of the COVID-19 pandemic on our clinical trial operations, please see the Risk Factor titled, "*The COVID-19 pandemic has affected and may continue to affect the initiation and conduct of our clinical trials, including the retention of patients for our GATHER2 clinical trial and patient recruitment and retention for our STAR clinical trial and the OLE study. It may have long-lasting effects on the conduct of clinical trials, which can make our ongoing and any future trials more difficult, costly or time consuming*."

- Third-Party Collaborators and Vendors. The pandemic has caused many of our third-party contract manufacturers, contract research organizations and other vendors to limit their operations and staff, which resulted in delays to some of our manufacturing and research and development activities. Over the past two years, several of our vendors have been facing backlogs due to work and demands from other clients, including those who were developing vaccines or medicines for the COVID-19 pandemic, which limited their availability to perform work for us. In addition, several of our vendors have experienced high levels of absenteeism due to variants of the virus and as a result scaled back their operations. At this time, we do not know whether there will be further impact on the work of our third-party vendors and collaborators due to the COVID-19 pandemic.

- Supply Chain and Materials. The pandemic has caused shortages, delays and disruptions in the global supply chain, including our contract manufacturers' ability to procure items, such as raw materials, that are essential for the manufacture of our product candidates. For example, the new manufacturer we are working with as a second source of supply for ACP drug substance has experienced issues with procuring a number of raw materials due to supply chain interruptions, which caused several delays to our manufacturing timelines with this manufacturer. We continue to monitor our supply chain closely.

The progression of the COVID-19 pandemic remains fluid and its impact on our business and operations remains uncertain. Many companies have been using force majeure clauses in their contracts to excuse or delay performing under their contracts, including as a result of supply chain interruptions. Our contract manufacturers, contract research organizations and other third parties on whom we rely for goods or services may make similar claims. If any such force majeure claims were successful, then not only would our timelines be delayed but also our right to recover for any economic damages due to the delay would be limited. Because we rely on many single-source suppliers, any such claims from them are likely to result in a delay to our timelines or otherwise adversely affect our operations or financial position.

The full extent to which the COVID-19 pandemic and other macroeconomic events, including the ongoing military conflict between Russia and Ukraine, will directly or indirectly impact our business, results of operations and financial condition will depend on developments that are uncertain and cannot be accurately predicted, including new information that may emerge concerning COVID-19 and new variants and subvariants of the virus, the actions taken to contain it or lessen its impact, and the economic impact on local, regional, national and international markets. We may experience additional disruptions to our clinical trials or supply chains, and reduced operations at third-party facilities, such as our clinical trial sites and suppliers, and delays in interactions with regulatory agencies or obtaining approvals for our product candidates. Although the current military conflict between Russia and Ukraine has not materially affected our business or operations, other geopolitical events and public health crises and natural disasters, such as future epidemics or pandemics or those resulting from the effects of climate change, may arise in the future. Any of these events may materially and adversely affect our business operations and financial condition.

Our strategy of obtaining additional rights to products, product candidates or technologies for the treatment of retinal diseases may not be successful. Although we entered into a license agreement with DelSiTech for its sustained release delivery technology, that technology may not be successful and/or we may not be successful in obtaining rights to and developing other sustained release delivery technologies for ACP.

An element of our strategy over the past few years 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 retina 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. For example, in June 2022, we entered into a license agreement, or the DelSiTech License Agreement, with DelSiTech Ltd., or DelSiTech, pursuant to which we obtained a worldwide, exclusive license under specified patent rights and know-how to develop and commercialize new formulations of ACP using DelSiTech's silica-based sustained release technology for treating diseases of the human eye. We plan to continue to evaluate additional opportunities to in-license or acquire products, product candidates and technologies on a selective and targeted basis, with a focus on potential additional sustained release delivery technologies for ACP that are promising and meet our criteria. We may also continue to consider other alternatives, including mergers, acquisitions, asset purchases or sales and/or other transactions involving our company as a whole or other collaboration transactions, including potential collaboration opportunities for further development and potential commercialization of ACP in one or more territories outside the United States. In December 2022, Opus acquired our rights, title and interests in and to our assets primarily related to our former product candidates IC-100 and IC-200. 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. For potential sustained release delivery technologies, that process

typically involves conducting a feasibility study of ACP formulated with the sustained release delivery technology and analyzing the resulting formulation, which can be time-consuming, costly and uncertain in outcome. If a formulation is promising based on the analytical results, we could then proceed to negotiate a longer term collaboration. For example, we in-licensed DelSiTech's silica-based sustained release delivery technology after reviewing feasibility results that we believe are promising; however, further testing and studies may undermine our belief. The process of proposing, negotiating and implementing a license or acquisition of a product candidate or technology is lengthy and complex. With respect to potential product candidates or technologies for which we have entered into option agreements, 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 option 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. More established companies may have a competitive advantage over us due to their size, cash resources and greater research, preclinical or clinical development, manufacturing 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. Other sustained release delivery technology companies that we are working with may be less willing to enter into long-term license or collaborations with us in light of our DelSiTech license. 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. For potential sustained release delivery technologies with ACP, we expect any promising technologies, including our in-licensed DelSiTech's silica-based sustained release delivery technology, would require extensive preclinical and clinical testing and investment in manufacturing before any potential approval by the FDA or other 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, regulatory 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 or in-licensing transactions;
- inability to receive regulatory clearance from government agencies, such as the Federal Trade Commission, to close transactions after announcement;
- 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, data or 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 approaches, 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.

Risks Related to Regulatory Approval of Our Products

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, recordkeeping, labeling, storage, 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. 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's 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 FDA issued guidance in March 2022 stating that it would treat co-packaged ophthalmic products, which generally consist of a drug component that provides the primary active pharmaceutical ingredient along with device components such as needles or syringes, as a combination product. We expect that our planned finished form of ACP drug product will be treated by the FDA as a combination product. We do not believe that this guidance has affected our strategy for obtaining FDA approval of ACP for the treatment of GA secondary to AMD.

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 and information concerning similar product candidates as our product candidates. 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 nonclinical, 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, for example aptamers such as ACP, manufactured using specialized 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 to date.

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.

Our intended regulatory pathway for obtaining marketing approval for ACP for GA is subject to several assumptions, including that we will be able to rely on the results from our GATHER1 and GATHER2 trials. To date, we have not had any formal interactions with the EMA regarding the GATHER1 or GATHER2 results or the contents of an MAA. We may decide to or may be required to collect additional data or conduct additional studies to seek or obtain approval for ACP for the treatment of GA secondary to AMD.

Based on the statistically significant results from our GATHER1 and GATHER2 trials and the safety profile of ACP to date, we believe we have sufficient data from two independent, adequate and well-controlled pivotal clinical trials of ACP in GA secondary to AMD to support an application for marketing approval. This belief is based on the assumption that a reduction in mean rate of GA growth over 12 months, measured by FAF based on readings at three time points: baseline, month 6 and month 12, is a primary endpoint of clinical relevance. The FDA, the EMA or other regulatory authorities may not agree with our view on the results of GATHER1 and GATHER2 and may require us to provide additional data or outcome measures. We may need to conduct additional clinical trials in order to obtain or maintain marketing approval. The FDA, the EMA or other regulatory authorities may also disagree with our conclusion regarding the robustness of the data from the GATHER1 and GATHER2 trials and may conduct their own sensitivity analyses yielding different results. If the GATHER1 and GATHER2 trials are not considered robust, or if regulatory authorities do not accept the study designs of GATHER1 or GATHER2, then in order to seek marketing approval we may need to conduct one or more clinical trials that meet the applicable regulatory requirements in order to obtain marketing approval.

Since receiving the 12-month results from the GATHER1 trial, we have not had any scientific advice or other formal interactions with the EMA or competent national authorities in the European Union or United Kingdom regarding the sufficiency of the GATHER1 and GATHER2 trials and results to support an application for marketing approval. We expect to have interactions with the EMA and MHRA during the first half of 2023 on our planned MAAs for marketing approval of ACP for GA. As we continue to engage with regulatory authorities, including in Europe, we may receive feedback that is not consistent with our expectations, including potential disagreements by the EMA and other regulatory authorities with what we understand are the requirements of the FDA. Regulatory authorities may require us to collect additional data, including additional functional vision data, conduct additional trials or take other actions in order to obtain marketing approval or reimbursement approval, which would require us to revise our development plans in those regions for ACP and delay our expected timelines.

Furthermore, serious adverse events may manifest as we continue to conduct our GATHER2 trial up to 24 months and in the OLE study for patients who completed their month 24 visits in the GATHER2 trial, in our STAR trial or in any other clinical trials we or a potential collaborator may undertake for ACP. When we follow patients for a longer period of time or collect safety data from a greater number of patients, such as with the OLE study, 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. There are a number of known safety risks associated with our product candidates and currently unknown safety issues may arise during development.*"

Our ongoing clinical trials and any future clinical trials or other studies for ACP that we or a potential collaborator may undertake may yield inconsistent safety or efficacy results with those we have observed to date or otherwise fail to demonstrate sufficient safety or efficacy to justify further development or to ultimately seek or obtain marketing approval. Any negative results from our ongoing or any future clinical trials or other studies for ACP will likely adversely affect our business and the value of your investment in our company.

Although we have obtained agreement with the FDA on a SPA for GATHER2, a SPA does not guarantee marketing approval of, or any other particular outcome from, regulatory review.

In July 2021, the FDA agreed to a SPA for GATHER2. Under the SPA procedure, the FDA provides a clinical trial sponsor with an official evaluation and written guidance on the design of a proposed protocol intended to form the basis for an NDA. A SPA agreement indicates concurrence by the FDA with the adequacy and acceptability of specific critical elements of the overall protocol design for a clinical trial intended to support a future marketing application, but it does not indicate FDA concurrence on every protocol detail. A SPA agreement also does not ensure the receipt of marketing approval or that the

approval process will be faster than conventional procedures. A determination regarding marketing approval is addressed during the review of a submitted NDA and depends on efficacy and safety results and an evaluation of the overall benefits and risks of treatment after review of the data from the development program in its totality.

Even after the FDA agrees to the design, execution, and analysis proposed in a protocol reviewed under the SPA process, the FDA may revoke or alter its agreement if a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun. A SPA agreement may also be changed through written agreement between the sponsor and the FDA. A revocation or alteration in our existing SPA could delay or prevent approval of our NDA for ACP. In addition, any significant change to the protocol for a clinical trial subject to a SPA would require prior FDA approval, which could delay implementation of such a change and the conduct of the related clinical trial. The FDA retains significant discretion in interpreting the terms of the SPA agreement and the data and results from any study that is the subject of the SPA agreement.

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 nonclinical 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 sold 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. If our third-party commercial partners fail to obtain marketing approval in certain jurisdictions, it may diminish the value of our product candidate to them and cause them to terminate their relationship with us.

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, and European Union rules and regulations ceased to apply to the UK starting on January 1, 2021. The Medicines and Healthcare products Regulatory Agency, or the MHRA, is now the sole decision maker for marketing authorizations of pharmaceutical products in the UK, except for Northern Ireland. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the UK the body of European Union law governing medicinal products that pre-existed before the UK's withdrawal from the European Union. 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. As a result of Brexit, we are planning to submit a separate application to the MHRA for marketing approval of ACP in the UK, in addition to the planned MAA for the EMA. 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 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 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 these designations if it believes that they are no longer supported by data from our clinical development program or for other reasons.

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 or for other reasons.

In April 2020, the FDA granted fast track designation to ACP for the treatment of GA secondary to dry AMD. Even though ACP has received fast track designation, we must continue to follow the requirements of the program in order to maintain the fast track designation, and even if we maintain the designation, we may not ultimately experience a faster development process, review or approval compared to conventional FDA procedures. The FDA's grant of fast track designation to ACP for the treatment of GA secondary to dry AMD does not imply that the FDA will grant fast track designation to ACP for another indication, or that the FDA will grant fast track designation for any of our other product candidates, if we choose to apply for fast track designation.

In February 2023, we also received a priority review designation from FDA for the use of ACP for the treatment of GA secondary to dry AMD. We may seek a priority review designation for one or more of our other product candidates. If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. These designations are within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meet the criteria for priority review, the FDA may disagree and instead determine not to make such designation. Further, even if we receive a designation, the receipt of priority review for a product candidate may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and such designation does not assure ultimate approval of the product by the FDA. In addition, even if one or more of our product candidates qualifies for priority review, the FDA may later decide that the product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

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. In November 2022, the FDA granted breakthrough therapy designation for ACP. 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 help design the clinical trials in an efficient manner.

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, 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 or similar 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 and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that

condition.

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, as the case may be, during that marketing exclusivity period from approving another marketing application for a product that constitutes the same or similar 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 may 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. In the European Union, the exclusivity period can be extended by two years following the completion of an agreed pediatric investigation plan. 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, or a competing sponsor may be allowed on the market, if any regulatory agency determines that the request for designation was materially defective or if the sponsor having orphan drug exclusivity 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 a competing sponsor's drug could nevertheless be approved for the same condition if certain requirements are met. 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 guidance stating that it would consider two gene therapy products to be different products if they express different transgenes or use different 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 by making a major contribution to patient care;
- 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.

The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved. We do not know if, when, or how the FDA or Congress may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business.

If the FDA, EMA or other foreign regulatory authorities approve generic versions of any of our product candidates that receive marketing approval, or such authorities do not grant our products appropriate periods of exclusivity before approving generic versions of those products, the sales of our products, if approved, could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "reference listed drug" in the FDA's Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials to

assess safety and efficacy. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labelling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug is typically lost to the generic product.

Generic drug manufacturers may seek to launch generic products following the expiration of any applicable exclusivity period we obtain if our products are approved, even if we still have patent protection for such products. The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for such product in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable regulatory exclusivity period, even if we still have patent protection for our product.

Competition that our products could face from generic versions of our products could materially and adversely affect our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in those products.

Risks Related to Manufacturing

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 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 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 ACP, IC-500 and any other product candidates that we may acquire or in-license. The manufacturing processes for our product candidates are technically complex. Problems with developing, executing or scaling up the manufacturing process could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims, insufficient inventory or delays to our programs. We may encounter problems achieving adequate quantities and quality of clinical-grade or commercial-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

We may encounter problems hiring and retaining scientific, manufacturing and quality assurance and control personnel needed to oversee our contract manufacturers, which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements. As our contract manufacturers scale 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, or may need to use alternative manufacturers. Resolving these issues could result in significant delays and may result in significantly increased costs. If we underestimate the demand for an approved product or the timing for the need for that product, given the long lead times required to manufacture or obtain regulatory approvals for our products and/or manufacturing facilities, 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 and other regulatory authorities, 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 ACP or any of our other product candidates. Failure by us or 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 with larger pharmaceutical companies. 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, including the effects of the COVID-19 pandemic on our 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, including to support potential commercialization. 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. The COVID-19 pandemic has affected our contract manufacturers' operations and the manufacture of our product candidates.*"

As we plan for the potential commercialization of ACP, we and our third-party manufacturers will need to complete several activities to ensure the continued supply of drug substance and drug product to support the future commercial supply of ACP. Any delay or failure in completing these activities could cause delays in its potential approval or could result in inadequate clinical or commercial product supply.

In order to obtain and maintain regulatory approval for ACP, our third-party manufacturers will be required to produce ACP drug substance with consistent quality and to execute fill/finish services on a repeated basis and document their ability to do so. In order for us to successfully commercialize ACP, if approved, our manufacturers also need to be able to produce quantities at a commercial scale. If our third-party manufacturers are unable to satisfy these requirements, our business would be materially and adversely affected.

We are working with our historical contract manufacturer Agilent to scale up and supply ACP drug substance for commercial use. Although Agilent has produced multiple batches at a larger scale, Agilent may not be successful in validating the manufacturing process for producing ACP drug substance at a larger scale. In parallel, we are working with a new contract manufacturer with the goal of assessing whether this manufacturer can produce ACP drug substance at adequate scale for commercial use. We experienced issues during technology transfer of the existing manufacturing process to the new manufacturer, which resulted in delays to our timelines with this manufacturer. Subject to successful completion of scale up and validation activities, we currently plan to use Agilent as the primary source of supply of ACP drug substance upon launch, if approved, and the new manufacturer as a second source of supply of ACP drug substance.

We are working with our historical manufacturer Ajinomoto for fill/finish and supply of ACP drug product with a new vial for commercial use. While we believe Ajinomoto has the capacity to supply us with ACP drug product with the new vial for our expected commercial supply needs upon launch, if Ajinomoto is unable to provide us and/or a potential collaborator with ACP drug product for potential commercial use, we will need to use alternative suppliers, which may increase our costs and delay our timelines. We are continuing discussions with Ajinomoto for long-term supply of ACP drug product and are assessing additional suppliers of ACP drug product.

In order to obtain regulatory approval for ACP, we expect we will need to demonstrate that the drug substance produced through the scaled up process, together with the finished drug product in the container closure system to be used commercially, are comparable to the drug substance and drug product we are currently using in our clinical trials. Under applicable regulatory guidance, comparability can be established through analytical, nonclinical or clinical data. Although we believe our plans and data to demonstrate comparability are sufficient for the FDA and potentially other health authorities, the FDA or other health authorities may disagree and require comparability data beyond what our plans currently provide for, which could impact our timelines to obtain regulatory approval for ACP.

We are continuing discussions with our supplier regarding a long-term supply agreement for the PEG starting material used to make ACP drug substance. However, we may not be able to agree to terms or may need to agree to unfavorable terms in order to secure adequate supply. While we believe this supplier has the capacity to supply us with the PEG at the scale that we will need for commercial manufacturing, if this supplier is unable to supply us the PEG in line with our expectations, we believe there are a limited number of alternative suppliers for this important starting material, and if we need to use those suppliers, it could increase our costs and delay our manufacturing plans for ACP.

Each of these activities is costly, time-consuming and uncertain in outcome. We may not be able to successfully validate the scaled up process for manufacturing ACP drug substance, or we may need to manufacture at a larger scale for our future commercial needs, demonstrate comparability of ACP drug substance manufactured through the scaled up process or comparability of the drug product in the container closure system to be used commercially, in each case, with the ACP

previously used in our clinical trials, or establish the long-term stability of the ACP drug product stored in the new vial container. The new manufacturers we have engaged or may engage in the future have not had previous experience with ACP and there may be additional issues with technology transfer. 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 ACP and to support potential commercial operations. In addition, we may not be able to secure adequate supply of ACP drug substance, including the PEG starting material used to make ACP drug substance, ACP drug product and finished goods for our future needs, including to support potential commercial launch, and we may need to secure alternative contract manufacturers or suppliers sooner than we currently expect. If any of the foregoing events occur, it could result in delays or increased costs to support our future development and commercialization of ACP.

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 oligonucleotides such as ACP.

We are continuing to establish manufacturing capabilities for IC-500. We are conducting additional formulation optimization activities.

We are working with a number of CDMOs to conduct scale up and cGMP manufacturing of the drug substance for IC-500 for early-stage clinical trials. We are working with a CDMO to conduct cGMP manufacturing and fill/finish of the drug product for IC-500 for our planned GLP toxicology studies and early-stage clinical trials. Our contract manufacturers have developed a manufacturing process for IC-500 drug substance and a formulated drug product. We are planning additional preclinical studies to optimize the dosage, delivery and formulation. Manufacturing, including process development, formulation development, drug substance and drug product manufacturing, can be costly and time-consuming. If we are unable to successfully manufacture and formulate IC-500 in line with our expectations, we may switch to a backup HtrA1 inhibitor or cease developing our HtrA1 inhibitor program altogether.

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.

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 and cGMP manufacturing, 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 cell banks or plasmids. In particular, plasmids 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, consistency in cell growth, productivity or cell line stability issues, product and process impurities, material shortages of any kind, shipping, distribution, storage and supply chain failures, cell culture contamination, equipment malfunctions, operator errors, facility contamination, labor problems, natural disasters, disruption in utility services, terrorist activities, epidemics and pandemics, 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. Although we were successful in releasing cGMP batches of our former product candidates IC-100 and IC-200 produced by a CDMO, we have not yet conducted any manufacturing activities, including process development, for any of our minigene research programs.

An important part of manufacturing drug products is performing analytical testing. Analytical testing of gene therapies involves tests that are more complex in scope and take a longer time to develop and to conduct as compared to those used for traditional drugs. We, our contract manufacturers and our contract research organizations need to spend 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 or released 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.

Risks Related to Product Commercialization

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.

Our business strategy is focused on developing transformative therapies for retinal diseases, including GA, intermediate AMD and a number of orphan inherited retinal diseases. There are multiple companies pursuing the development of therapeutics targeting the complement pathway for age-related retinal diseases. Some of them have better name recognition, more resources and a longer history of developing therapies than we do. Competition in this field is intense and especially 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 limit the commercial opportunity for our product candidates. For example, Apellis's complement protein C3 inhibitor product, pegcetacoplan, was approved by the FDA in February 2023 for the treatment of GA secondary of AMD.

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 ACP, 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. Our competitors may also be pursuing similar lifecycle management programs, such as sustained release delivery technologies. 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.

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 personnel, establishing clinical trial sites and enrolling patients 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 competitive products and programs. Other competitive programs may exist of which we are not aware.

Competitive considerations for GA or dry AMD:

- In February 2023, the FDA approved Apellis Pharmaceuticals, Inc., or Apellis’s, pegylated, synthetic peptide targeting complement protein C3, pegcetacoplan, for the treatment of GA secondary to AMD. This product has a dosing regimen of once every 25 to 60 days. In December 2022, Apellis submitted an MAA to the EMA. Apellis announced that the EMA had validated their MAA and the application was under review, with a decision expected in early 2024.
- We are aware that LumiThera, Inc. has a medical device using its LT-300 light delivery system, which is approved in the European Union for the treatment of dry AMD. In addition, there are a number of products in preclinical and

clinical development by third parties to treat GA or 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 AstraZeneca PLC (which acquired Alexion Pharmaceuticals, Inc. in 2021), Akari Therapeutics, Plc, Annexon Inc., Apellis, Applied Genetic Technologies Corporation, or AGTC, Biogen Inc., Gemini Therapeutics, Inc. (which merged with Disc Medicine, Inc.), Gyroscope Therapeutics (which was acquired by Novartis AG), IONIS Pharmaceuticals, Inc. (in collaboration with Roche AG), Janssen Pharmaceuticals Inc. (which acquired its program through the acquisition of Hemera Biosciences, LLC), Kanaph Therapeutics Inc, NGM Biopharmaceuticals Inc. and Novartis AG each have complement inhibitors in development for GA or dry AMD, including, in the cases of Gyroscope Therapeutics and Janssen Pharmaceuticals, complement inhibitor gene therapies and in the cases of AGTC and Gemini Therapeutics, research programs on complement factor H gene therapy. We believe that the most advanced of these programs is Apellis's, as described above. Moreover, we are aware that several other companies, including Allegro Ophthalmics, LLC, Alkeus Pharmaceuticals Inc., Astellas Pharma Inc., Aviceda Therapeutics, Boehringer Ingelheim, Lineage Cell Therapeutics, Inc. (which was acquired by Roche AG), Ocugen, Inc., ONL Therapeutics, Inc., Regenerative Patch Technologies, Roche AG, Stealth BioTherapeutics Corp. and Visus Therapeutics, are pursuing development programs for the treatment GA or dry AMD using different mechanisms of action outside of the complement system, including Genentech, Inc. (an affiliate of Roche AG) and Gemini Therapeutics, which are pursuing HtrA1 inhibition as a mechanism of action. We believe that the most advanced HtrA1 inhibitor program in development was Genentech's monoclonal antibody HtrA1 inhibitor, which was being studied in a Phase 2 clinical trial until it was discontinued in October 2022.

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 AGTC, Alkeus Pharmaceuticals, Inc., Beam Therapeutics Inc., Biogen, Generation Bio Co., Kubota Vision Inc. (formerly Acucela), Lin BioScience, Inc., ProQR Therapeutics N.V., or ProQR, and Spark Therapeutics (a subsidiary of Roche AG) each have research or development programs in Stargardt disease. Three of these programs, Alkeus, Kubota and Lin BioScience, are exploring the use of oral therapeutics, while AGTC, Nightstar and Spark are each using a gene therapy approach, Beam is using a base editing approach, and ProQR is using an RNA-based approach. Kubota’s product candidate, to which the FDA and the EMA granted orphan drug designation in August 2020, is in Phase 3 development while Alkeus’s product candidate is in Phase 2 development. In addition, several academic organizations have early stage programs in Stargardt disease.

Competitive considerations for LCA10:

- We are aware that Editas Medicine, Inc. has a gene editing program for LCA10, for which a Phase 1/2 clinical trial is ongoing, ProQR is developing an RNA-based therapeutic for LCA10 that is currently in Phase 2/3 development, Generation Bio Co. has a preclinical program that utilizes close ended DNA 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 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., Odylia Therapeutics and Wave Life Sciences, Inc. are exploring potential programs in *USH2A*-related IRDs.

If we are unable to establish sales, marketing and distribution capabilities, we may not be successful in commercializing ACP or any of our other product candidates, if and when any such product candidate is approved. We may encounter difficulties hiring and effectively deploying a sales force.

As a company, we have no experience in the sale, marketing or distribution of pharmaceutical products. We continue to hire commercialization personnel, including field-based sales personnel, and planning and are setting up a sales, marketing and distribution infrastructure. Our commercial strategy for ACP and any other product candidates that may obtain approval, 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, will 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 is approved, the territories in which the product may be marketed and the commercial potential for such product candidate. In addition, our commercial strategy would vary depending on whether the disease is typically treated by general ophthalmology practitioners or specialists, such as retinal specialists, and the likely degree of acceptance of our product candidate by the relevant physicians in various markets. At this time, we are planning to sell, market and distribute ACP, if approved for GA, in the United States ourselves.

There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a qualified 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; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to build internal sales, marketing and distribution capabilities, then we would need to outsource to third parties, which carries its own risks. If we do not or are unable to 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 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 other approved products on the market and/or 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 to or by a subgroup of patients;
- for treatment regimens calling for multiple intravitreal injections on the same day, restrictions in the label imposing a waiting period between intravitreal injections;
- our and any commercialization partner's ability to offer our products at competitive prices;
- availability and timeliness 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 and physicians to try new therapies, particularly in light of the existing available standard of care or to the extent our product candidates require invasive procedures for administration;
- prevalence and severity of any side effects or perceived safety concerns, such as CNV; and

- whether competing products or other alternatives are more convenient or easier to administer, including alternatives that offer a less frequent dosing regimen than monthly intravitreal injections, in the case of ACP, come to market. For example, Apellis's pegcetacoplan was approved with a dosing regimen of every 25 to 60 days, which physicians and patients may view as more convenient than a potential monthly dosing regimen for ACP, if approved.

Our development program for ACP in GA uses an anatomical primary endpoint, the mean rate of growth (slope) estimated based on GA area over 12 months. We believe that this efficacy assessment is most likely to demonstrate clinical relevance for an investigational product across a heterogeneous GA patient population. Patients, physicians and payors may not recognize the value of, and we may not obtain marketing or reimbursement approval in certain jurisdictions outside the United States for, ACP based on the anatomical data we expect would be included in the label for ACP, if approved. To date we have limited functional vision data from the GATHER1 and GATHER2 trials, and the data we have is from a post hoc exploratory analysis. If approved, we may not be able to include the limited functional data we have generated to date in the label for ACP, and we may not be able to use such data for promotional purposes.

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, market response to anti-VEGF agents currently approved for treatment of wet AMD, third-party research reports and other surveys. The potential market opportunity for our product candidates may also differ across geographies. While we believe that our internal assumptions are reasonable, 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 are 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. 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 GA, likely will diminish the therapeutic benefit conferred by a new drug product due to irreversible cell death. 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 ACP in GA and for many countries in Europe, we may need to demonstrate a relative benefit in functional vision 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. 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, as seen recently with a number of gene therapies that entered the market. Moreover, if we obtain marketing approval for a product candidate, such as ACP, in more than one indication, including, for example in an orphan indication such as STGD1 and a non-orphan indication such as GA, 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 experienced by the pharmaceutical industry may be further exacerbated by legislative and policy changes under consideration by the Biden Administration, the U.S. Congress and many states. See later in the Risk Factors section for a discussion of the expected impact of the Inflation Reduction Act and other drug pricing developments. We expect that ACP, if approved for GA, would be reimbursed in large part by Medicare Part B and therefore, these cost containment measures will likely affect our pricing and reimbursement strategies.

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, which are generally covered by the "buy and bill" reimbursement model under Medicare Part B. We may choose to, or be required by market dynamics to, implement access and reimbursement policies that may not be successful in driving use of and reimbursement for our products, if approved. We or any commercialization partner may also 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. 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 costs. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent, which could delay physicians' use of our products. 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, which many members of the U.S. Congress expressed an interest in pursuing. In September 2020, HHS issued a rule permitting limited importation of drugs from Canada. 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 financial condition, or our ability to raise capital needed to commercialize products.

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;

- withdrawal of clinical trial participants;
- injury to our reputation and significant negative media attention;
- 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 partner were to become subject to product liability claims or were unable to successfully defend themselves against such claims, any such commercialization partners could be more likely to terminate such relationship with us and therefore substantially limit the commercial potential of our products.

Risks Related to Product Development

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 candidate in humans. Prior to initiating clinical trials, we 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 pursuing, may never yield a product candidate for preclinical or clinical development. Early stage and later stage research experiments and preclinical studies, including the feasibility studies and analytical testing we are performing for potential sustained release delivery technologies for ACP and the preclinical studies we are conducting and planning to conduct for IC-500, may fail at any point or produce unacceptable or inconclusive results 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 a statistically significant efficacy signal. 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;
- 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 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 or quality of starting materials, such as the polyethylene glycol, or PEG, used for the manufacture of ACP, and issues with the packaging, distribution, storage and import/export of materials and products;

- we or our contract research organizations may be unable to complete necessary analytical method development or qualification for testing our product candidates;

- we may not be able to successfully scale up or validate a manufacturing process for one or more of our product candidates, including the manufacturing process for ACP, and may need to rely on second source suppliers for adequate supply of drug substance and/or drug product in line with our needs and expectations;

- 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 clinical trials for orphan or other rare diseases;

- we, through our clinical trial sites, may not be able to maintain enrolled patients for scheduled visits and treatments, or to retain patients altogether, especially in light of the COVID-19 pandemic, which could result in missing data from our clinical trials, potentially leading to uninterpretable results or a clinical trial not being sufficiently powered to demonstrate an efficacy benefit;

- 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 in the European Union or for Stargardt's disease, LCA10 or Usher's syndrome in either the United States or the European Union, the regulatory pathway for product candidates in those indications, including the selection of efficacy endpoints and their clinical meaningfulness, is subject to review and acceptance by various regulatory authorities;

- 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 or nonclinical studies 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. This risk 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, including the costs of manufacturing activities to support those clinical trials, 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 otherwise change our clinical development plans, 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 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. The progress of our clinical trials may be dependent on macro-economic events beyond our control, such as the COVID-19 pandemic. For example, the pandemic and governmental measures instituted in response to the pandemic have caused a number of missed visits in the GATHER2 trial and may cause additional patients to miss visits or drop out of the trial, which could result in missing data from this trial. Furthermore, our development plans may change based on feedback we may receive from regulatory authorities throughout the development process or for other reasons. 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 ACP 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 ACP in the indications we are pursuing or in any other indication we may choose to pursue.

We are currently targeting GA associated with various stages of AMD including intermediate AMD and STGD1 with ACP. 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 there is nonclinical scientific literature supporting the potential use of complement system inhibitors for the treatment of STGD1, we have not yet completed a clinical trial assessing ACP for the treatment of STGD1 and do not have any unmasked data regarding the efficacy of ACP in this indication. As a result, this approach may not prove successful.

ACP is designed to inhibit complement protein C5. There are no FDA or EMA approved products that utilize C5 inhibition as a mechanism of action to treat GA or STGD1. Although Apellis's complement protein C3 inhibitor was recently approved by the FDA for the treatment of GA, there have been other investigational products using complement inhibition as a mechanism of action for the treatment of GA, including inhibition of C5, that ultimately proved to be unsuccessful.

Our plans to pursue ACP in intermediate AMD are based on results from post-hoc analyses of data from our GATHER1 trial, as well as the GATHER1 and GATHER2 clinical trial data included in our NDA. Although there is scientific literature to support the potential use of complement system inhibitors for the treatment of intermediate AMD, we have not yet conducted, and currently do not plan to conduct, a clinical trial evaluating ACP in patients with earlier stages of AMD. Intermediate AMD is a developing field of study whose patient population continues to be defined by the medical community. We are continuing discussions with the FDA on using the GATHER1 and GATHER2 clinical trial data included in the current NDA submission to support treatment of GA associated with earlier stage disease, including in patients with intermediate AMD. We may also decide to pursue clinical development of ACP for other indications, including those we previously studied

such as wet AMD and IPCV. Similar to GA and STGD1, ACP, and the use of C5 inhibition, are unproven in those indications and we may not be successful in our efforts to develop ACP for those indications.

The GATHER2 trial may yield 24-month results that are different from the positive 12-month results we observed or the results from the GATHER1 trial. Additionally, the OLE study may yield safety results that are different from the safety data we have to date for ACP.

The positive 12-month results we observed from the GATHER2 trial may not be consistent with the 24-month results of this trial. In accordance with the GATHER2 trial protocol, we will continue to treat and follow patients through the 24-month time point to collect additional data. These data may indicate an unexpected or unknown safety issue, including increased incidence of CNV, or may indicate a different efficacy profile for ACP during the period between month 12 and month 24. After month 24, 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 either the ACP 2 mg group or the sham control group. Additionally, patients may drop out from the trial or miss visits between month 12 and month 24 in a greater number than we expect, which could also hamper our ability to draw conclusions from the 24-month data. If the month 24 results are inconsistent with the month 12 results, it may affect our ability to commercialize ACP for GA, or to obtain marketing approval or reimbursement approval for ACP in certain jurisdictions outside the United States.

Additionally, for our GATHER2 trial, we have re-randomized the patients in the monthly ACP 2 mg treatment arm at 12 months and are evaluating dosing ACP 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 GATHER2 trial, however, is not designed to assess any differences we observe between these treatment groups at 24 months with statistical significance and the label we would seek for ACP in GA will be based on the primary endpoint at 12 months and in all likelihood provide for monthly administration of ACP.

We are conducting the GATHER2 trial at many clinical trial sites and in many countries that were not included in the GATHER1 trial. The introduction of new sites, as well as the resulting different patient demographics, have resulted in additional variability in the conduct of the trial and variability of patient outcomes. For example, although we observed a 14.3% reduction in the mean rate of growth (slope) in GA area between the ACP 2 mg group and sham control group at 12 months across the entire trial using the primary analysis, in a post-hoc analysis of U.S. only patients, we observed a 25.5% reduction. We may encounter additional variations as we continue to analyze the data.

Unlike the GATHER1 or GATHER2 trials, all patients participating in the OLE study will receive monthly doses of ACP 2 mg, regardless of the treatment arm (ACP or sham procedure) that they were randomized to in GATHER2. The safety results from the OLE study may be different from the safety results we have to date for ACP.

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. There are a number of known safety risks associated with our product candidates and currently unknown safety issues may arise during development.

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 drugs that initially showed promise in clinical or earlier stage testing have later been found to cause side effects that prevented further development or future commercialization. Safety issues may arise due to reasons unrelated to the study drug, such as issues with the injection procedure or the syringes or needles being used.

We observed an increase in the number of investigator-reported cases of CNV in the ACP treatment groups in the completed GATHER1 trial as compared to the sham control groups. In the ongoing GATHER2 trial, we have observed a higher rate of CNV cases in the ACP 2 mg treatment group as compared to the sham control group at 12 months. We have no unmasked data regarding the safety, tolerability or efficacy of ACP administered for the treatment of STGD1. We have no human data regarding IC-500.

Although we view the rate of CNV incidence in the ACP 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 ACP may

increase the risk of patients developing CNV to an unacceptable degree. Moreover, our clinical trials for ACP involve multiple intravitreal injections over an extended period of time and, as such, may involve risks involved with 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 ACP. Although we have observed no events of endophthalmitis, no intraocular inflammation events, no events of vasculitis and no ischemic optic neuropathy events through month 12 in GATHER2, these events may occur in the second half of the trial or in the OLE study. An unforeseen or unexpected safety event, or any safety finding that is inconsistent with our prior experience with ACP, from any of our clinical trials for ACP, including from the GATHER2 trial during which we will follow patients and collect safety data over 24 months or the OLE study during which we will follow patients and collect safety data for up to an additional 18 months, may impact the long-term viability of ACP as a potential treatment for GA, STGD1 or any other indication for which we may seek to develop ACP.

As HtrA1 inhibition is a novel treatment approach for treating ocular disease, this treatment approach may present potentially unknown safety risks when tested in clinical trials that could not have been anticipated based on preclinical studies. In addition, we intend to administer IC-500 by intravitreal injection, which poses the same safety risks outlined above with respect to intravitreal injections of ACP.

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 surgeons must repeat the same subretinal injection procedure in multiple patients with consistency across patients and surgeons. In the event that we progress into clinical development with a gene therapy product candidate, 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.

We have no unmasked clinical data regarding the safety and efficacy of ACP as a treatment of STGD1. The dropout rate or patients with missing visits may reduce the number of patients from whom we can collect and analyze data from STAR. We may not be able to recruit additional patients for this trial in line with our expectations.

We have no unmasked clinical data regarding the safety and efficacy of ACP as a treatment for STGD1. As STGD1 is an orphan indication, to our knowledge there is only very limited natural history data currently available regarding the variability of 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 ACP, and not necessarily to reverse prior degeneration or restore visual function, patients participating in our STAR trial, who are generally younger and may experience vision loss that is more subtle than patients with GA or other forms of AMD, may not perceive a benefit from enrolling or continuing to participate and therefore may drop out of this trial or miss scheduled visits and treatments. Although we and the investigators and their staffs take efforts to encourage continued patient participation, the dropout rate may exceed our expectations. A higher than expected dropout 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 STAR trial could be underpowered to demonstrate a potential clinical benefit for ACP in STGD1 with statistical significance.

We have decided to enroll approximately 25 additional patients in this trial, with the goal of enrolling a total of approximately 120 patients. This change to the trial has increased the costs associated with this trial and has delayed the

timelines for receipt of data from this trial. We believe an expanded trial could allow us to collect additional data regarding the effect of ACP on STGD1 patients and help us mitigate the risks from additional patient dropouts and missed visits; however, these expectations may prove to be incorrect. Patient recruitment may take longer or cost more than we would expect.

The COVID-19 pandemic has affected and may continue to affect the initiation and conduct of our clinical trials, including the retention of patients for our GATHER2 clinical trial and patient recruitment and retention for our STAR clinical trial and the OLE study. It may have long-lasting effects on the conduct of clinical trials, which can make our ongoing and any future trials more difficult, costly or time consuming.

Our GATHER2 and STAR trials and the OLE study involve sites located across the United States and in many countries outside the United States. In early 2020, we made a number of operational changes to our clinical trials as a result of the COVID-19 pandemic, its effects on current and prospective participating patients, and various governmental and other measures in response to the pandemic. As the COVID-19 pandemic evolves, we may make further changes to how we conduct our ongoing and any future clinical trials.

Patient enrollment, missed patient visits and patient retention remain key risks for our clinical trials. Due to the COVID-19 pandemic, we delayed the initiation of patient enrollment for the GATHER2 trial from March 2020 to June 2020. We are continuing to enroll patients in the STAR trial and the OLE study, where we may choose to or be required to slow down or stop patient enrollment in certain geographies due to the COVID-19 pandemic and any governmental measures taken in response. Patients, in turn, may be reluctant to enroll in clinical trials or to maintain their scheduled visits and treatments once enrolled due to their reluctance to visit clinical trial sites for fear of potential exposure to COVID-19 or ongoing restrictive measures requiring social distancing or limiting travel. These concerns may particularly apply to GA patients, many of whom are elderly and therefore at a higher risk for COVID-19 and other diseases than the general population.

For patients who are enrolled in our trials, the COVID-19 pandemic may cause them to miss study visits or drop out in greater numbers than expected, which could affect our ability to complete our trials and obtain data in accordance with our expectations. Compared to the generally elderly patients in our GATHER2 and OLE trials, the patients in the STAR trial are generally younger and have work and family commitments, which may cause them to miss more visits or drop out in greater numbers. In addition to the risks posed by increased patient dropouts, if patients miss scheduled visits in greater numbers as a result of the pandemic, especially if a patient misses consecutive visits, it may affect our ability to draw meaningful conclusions from the clinical data. We are aware that a number of patients initially enrolled in the STAR trial missed consecutive visits during the early months of the COVID-19 pandemic and that a number of patients in our Latin America sites for GATHER2 missed visits because of the COVID-19 pandemic. Although we have not experienced any material impacts on our clinical trials from the COVID-19 pandemic in 2022, we do not know yet whether the number of missed visits will increase in any of these trials, and whether and to what extent missed visits may impact patient retention in these trials or the results of the trials, especially since we are masked to the data until the conclusion of the trials. The duration of the GATHER2 and STAR trials, and of the OLE study, at 24 months, 18 months and 18 months, respectively, plus time for recruiting patients, makes them more likely to be affected by any subsequent waves of the COVID-19 pandemic.

The COVID-19 pandemic initially caused many of our clinical trial sites and competent health authorities and ethics committees in certain countries to reduce their staff and operations. In 2020, this reduction in operations resulted in delays to the approval of and the site activation process for the GATHER2 trial in certain geographies. During late 2020 to early 2021, a number of our clinical trial sites scaled back their operations because of surges in COVID-19 cases or new lockdown measures being imposed. If any reductions in staff and operations recur or persist at our clinical trial sites, it may affect our conduct of the ongoing GATHER2 and STAR trials and the OLE study. Shortages of vaccines, personal protective equipment and other supplies for the prevention of COVID-19 and the proliferation of new variants of COVID-19 may cause our clinical trial sites to further scale back the number of staff on site and other operations, and may also cause prospective or enrolled patients to avoid clinical trial visits.

In addition to the disruptions to the operations of many clinical trial sites, the COVID-19 pandemic affected our monitoring and audit operations, for example, by requiring remote monitoring, remote source document verification and remote auditing in many instances. Some countries prohibit or limit remote source document verification due to privacy and other concerns. Although we do not believe the COVID-19 pandemic has materially affected the robustness of our data verification process for the GATHER1 or GATHER2 trials, we or regulatory authorities may find data verification discrepancies upon reviewing the data from the trials. This risk may also affect our data verification processes for the STAR trial or the OLE study.

Our development of IC-500 is also based on a novel mechanism of action that is unproven and poses a number of scientific and other risks.

IC-500, our selected product candidate from 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 IC-500, and this mechanism of action may not prove safe and effective for these diseases. Although we are aware that a few other companies are pursuing HtrA1 inhibition as a strategy for treating retinal diseases, to date, there is limited published clinical data regarding the safety and efficacy of HtrA1 inhibition in the target patient population. We are also aware that Genentech was conducting a Phase 2 clinical trial for its monoclonal antibody HtrA1 inhibitor but discontinued that trial in October 2022. We made the decision to acquire our HtrA1 inhibitors program in 2018 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. Even though genetic and histologic findings correlate HtrA1 with AMD, the development and progression of AMD may not be affected by HtrA1 or may be more strongly affected by other genes. Our hypothesis that targeting inhibition of HtrA1 may be a safe and effective method of treating AMD may ultimately be incorrect, which would likely adversely affect the value of IC-500 and its continued development.

To our knowledge, there are no suitable animal models for GA or dry AMD. This absence of a suitable animal model makes designing a proof of concept study to assess the preclinical efficacy of IC-500 difficult. To date, we have only generated limited preclinical data of IC-500 in animal studies and we are conducting and planning additional preclinical studies, which ultimately may fail to produce favorable results. In addition, we have not had any formal or informal interactions with the FDA or other regulatory authorities regarding our development plans for IC-500. We do not know whether the FDA or other regulatory authorities will accept any preclinical proof of concept study we may propose, or other aspects of our development plans for IC-500. The FDA may require us to change our plans or conduct additional studies, which would increase our costs and delay our timelines.

Gene therapy is an emerging field of drug development that poses many scientific and other risks. Our limited experience with gene therapy 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 a small number of 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 processes and materials, 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. For example, we observed inconclusive data across the two preclinical toxicology studies we conducted for our former product candidate IC-100, which caused us to evaluate our development options for this product candidate. 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 our miniCEP290 program and other minigene programs, we are pursuing 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 and miniABCA4 programs are in mice models for LCA10 and STGD1, respectively, 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 research efforts 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 gene therapy research programs 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.

As we pursue our gene therapy research programs, we expect we will need to continue to grow our own gene therapy scientific and technical capabilities through hiring internally and 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 any promising product candidates that emerge from our gene therapy research programs.

We have not previously conducted any clinical development involving gene therapies and, if and when we are ready to conduct 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. Many of the indications for which we are pursuing our gene therapy programs have limited natural history data and limited number of therapies in clinical development, which may make selecting an appropriate endpoint difficult. Furthermore, our gene therapy programs are targeting orphan diseases with relatively small populations, which limits the pool of potential patients for our gene therapy clinical trials. Because gene therapy trials generally require patients who have not previously received any other therapy for the same indication, we will also need to compete for the same group of potential clinical trial patients with our competitors who are also developing therapies for these same indications. 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."*

Ethical, legal and social issues related to genetic testing may reduce demand for any product candidates that require genetic testing for use.

For certain of our product candidates, including any promising candidates from our gene therapy research programs, we may require that as part of participating in a clinical trial or determining eligibility for that product candidate, patients undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. The ownership of and the lawfulness of using 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 or receive a product candidate for which we require genetic testing.

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, including to support potential commercialization of ACP. 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. 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 starting materials and other specialized components of production used in the manufacture and fill/finish of our product candidates.

We have historically relied on, and purchased on a purchase order basis from, a single third-party manufacturer, Agilent, to provide ACP drug substance. We are working with Agilent and a new manufacturer to conduct scale up and validation activities for ACP drug substance. Subject to successful completion of scale up and validation activities, we currently plan to use Agilent as the primary source of supply of ACP drug substance upon launch, if approved, and the new manufacturer as a second source of supply of ACP drug substance. We are continuing discussions with Agilent for long-term supply of ACP drug substance. We have also historically relied on a single third-party manufacturer, Ajinomoto, for ACP drug product. We plan to rely on Ajinomoto for supply of ACP drug product using the new vial for commercial supply upon launch, if approved.

We are continuing discussions with Ajinomoto for long-term supply of ACP drug product and exploring additional suppliers of ACP drug product. We purchase the PEG starting material on a purchase order basis from a single third-party supplier. We are continuing discussions with this supplier for a long-term supply agreement for the PEG starting material. We also engaged a manufacturer to package ACP drug product and produce finished goods for potential commercial distribution. For these and any other manufacturers with which we do not have any contractual commitments for supply, the pricing and other terms for supply may vary, even substantially, over time and could adversely affect our financial results and operations.

For IC-500, we work with a number of CDMOs to conduct process development, scale-up and cGMP manufacture of the drug substance and drug product for preclinical toxicology studies and early-stage 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 production constraints, 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. We may not have adequate or timely visibility over issues at our third-party manufacturers, and may not become aware of any such issues until the effect on our programs, if any, has already materialized.

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 may need to do so under unfavorable terms. Furthermore, there are a limited number of contract manufacturers with experience manufacturing oligonucleotides, which may limit our ability to find and use alternative manufacturers.

As a result of the COVID-19 pandemic, our third-party contract manufacturers and many sole-source suppliers initially limited their operations by reducing the number of staff on site and instituting restrictions on visitors. These changes affected how we work with our manufacturers and resulted in minor delays to the progress of our manufacturing activities. Additionally, shortages and governmental restrictions arising from the COVID-19 pandemic have disrupted and may continue to disrupt the ability of our contract manufacturers to procure items, such raw materials, which are essential for the manufacture of our product candidates. Over the past two years, disruptions in the global supply chain for various materials, due to the effects of the COVID-19 pandemic and other macro-economic events, have caused order backlogs or shortages. For example, the new manufacturer we are working with as a second source of supply for ACP drug substance has experienced issues with procuring a number of raw materials due to supply chain interruptions, which caused several delays to our manufacturing timelines with this manufacturer. To date, we have not experienced any drug product supply issues impacting our GATHER2 and STAR clinical trials or the OLE study and we do not believe our overall timelines for ACP have been materially impacted as a result of supply chain issues affecting our contract manufacturers. We continue to monitor our supply chain closely.

In addition, we and our third party manufacturers source some of the raw and starting materials used in the manufacture of our product candidates from outside the United States. We source the PEG starting material from a supplier 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, and other geopolitical events such as the military conflict between Russia and Ukraine and the resulting sanctions imposed by the United States and other governments and any additional future sanctions or actions in response to the military conflict or other geopolitical events, 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 control and quality assurance;
- 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, or the proprietary information of third parties that we are responsible for protecting; and

- the possible termination or non-renewal 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. As part of seeking marketing approval, we and our third-party manufacturers will be subject to inspections by the FDA and other regulatory authorities. 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 plan to rely on third-party commercial distribution and other commercial services vendors to assist us with the development and implementation of our commercial value chain and related services for the potential commercialization of ACP, if approved, and those third parties may not perform satisfactorily, including lacking adequate workforce and capacity for storage and distribution.

We plan to rely on third parties, such as commercial packaging and warehousing providers, third party logistics providers, or 3PLs, specialty distributors and specialty pharmacies, for the storage and commercial distribution of ACP, if approved. We also plan to rely on third party access and reimbursement providers to support patient access and provider reimbursement programs for ACP, if approved. Those third parties may have different business priorities and may also have relationships with other entities, some of which may be our competitors. If we need to enter into alternative arrangements, our commercial value chain could be adversely affected and our commercialization efforts could be delayed.

The COVID-19 pandemic has resulted in persistent global supply chain challenges and logistics backlogs for many industries. Our selected commercial service providers may experience worker shortages, distribution backlogs or other issues that could disrupt our ability to meet product demand. Any performance failure on the part of these third parties could delay commercialization of ACP, if approved, and adversely affect our 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 follow regulatory requirements or 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, medical institutions (including reading centers) and clinical investigators, in conducting our preclinical testing, analytical testing and clinical trials for our product candidates. We also expect to rely upon certain facilities at UMMS for various services supporting our research and development programs, including maintenance and care of research animals and production of viral vectors. 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.

The COVID-19 pandemic has affected the work of our outside vendors and collaborators. For example, during 2020 UMMS suspended researcher access to their laboratories and the conduct of certain animal studies and reduced the number of staff in its animal medicine department, which delayed our timelines for our miniCEP290 and miniUSH2A sponsored research programs. Shortages and governmental restrictions arising from the COVID-19 pandemic may also disrupt the ability of our clinical trial sites and other contract research organizations to procure items that are essential for our research and development activities, including, for example, medical and laboratory supplies used in our clinical trials, including personal protective equipment for site staff, or animals that are used for preclinical studies. For example, there have been shortages of various animals used in research studies, such as several types of monkeys, which are typically sourced from China, due to the COVID-19 pandemic and disruptions to the global supply chain. Since 2021, several of our vendors have been facing backlogs due to work and demands from other clients, including those who are developing vaccines or medicines for the COVID-19 pandemic, which has limited their availability to perform work for us. There is no guarantee that the COVID-19 pandemic will not further impact our third-party vendors, which could have a material impact on our research and development programs.

Our reliance on these third parties for preclinical testing, analytical 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 and other regulatory authorities require 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 various government-sponsored databases within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Over the past decade, 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. In 2020 and early 2021, the COVID-19 pandemic prevented us from performing audits on our vendors and clinical trial sites that we otherwise would have performed, which decreases the level of oversight we have over those vendors and clinical trial sites and increases the risk of non-compliance. 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. For a number of our analytical development and testing providers, our CDMOs subcontract and manage that work on our behalf and we have less visibility into or control over their activities. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies, analytical testing 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. Our product candidates are required to be stored and shipped at certain temperatures and a deviation from those requirements may result in delays or additional costs. 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 plan to seek a collaborator for the further development and potential commercialization of ACP in one or more territories outside the United States. If we are not able to establish collaborations for ACP or for any of our other 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 and the hiring of additional qualified personnel. In addition, the development or 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. A number of countries require sponsors to perform a clinical trial in the local jurisdiction or with patients similar to the demographics of the local population as a condition to approving the drug. 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 plan to seek a collaborator for the further development and potential commercialization of ACP in one or more territories outside the United States.

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 and other data we have generated for the product candidate, 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, any patent or other forms of exclusivity for such product candidate and 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, the ability to obtain governmental approval for the collaboration, if necessary, and industry and market conditions generally. For a potential collaborator for a sustained release delivery technology for ACP, those factors may include an assessment of the technical feasibility of the technology using the data we and the potential collaborator have generated, which may be preliminary and limited. 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. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of business combinations among pharmaceutical and biotechnology companies over the past decade that have resulted in a reduced number of potential future collaborators and this trend is likely to continue.

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 in line with our expectations. For ACP, if we choose to and are unable to find a collaborator for potential commercialization outside the United States, we likely will need to raise additional capital, hire additional personnel and undertake the effort ourselves, any of which may be unsuccessful. In addition, although we currently intend to commercialize ACP in the United States ourselves, if approved, as part of the process for finding a collaborator for potential commercialization in one or more territories outside the United States, we may choose to grant a potential collaborator co-commercialization or co-promotion rights in the United States.

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, including sustained release delivery technologies for ACP. 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 enter into any arrangements with third parties, 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 de-emphasize 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;
- collaborators may make pricing, reimbursement and commercial decisions that adversely impact or reduce our flexibility to employ pricing, reimbursement and commercial strategies in other geographies, including the United States;
- we could grant exclusive rights to our collaborators, which would prevent us from collaborating with others;
- we may be obligated to supply the collaborator with drug substance or drug product in an amount sufficient for its needs, or may be dependent on the supply of certain materials or products by the collaborator;

- disagreements or disputes with collaborators, including disagreements or disputes over proprietary rights, contract interpretation or the preferred course of development or commercialization, 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 expensive, and be uncertain in outcome;

- 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 agree to other conditions that are not attractive to us; and

- collaborations may be terminated at 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 ACP and our miniCEP290 program. These license arrangements, as well as the Inception 4 Merger Agreement, impose diligence obligations on us. We depend on research licenses from UMMS for our miniABCA4 and miniUSH2A programs. We may enter into similar arrangements for 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 ACP. We are party to the DelSiTech License Agreement with DelSiTech for rights to develop and commercialize new formulations of ACP using DelSiTech's silica-based sustained release delivery technology. 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. For our miniCEP290 program, we are party to an agreement with UMass, under which we must meet certain milestones by certain timelines and if we fail to do so, we may need to expend significant amounts of money to extend those timelines or otherwise be in breach of that agreement and UMass would then have the right to terminate the agreement and we could lose our rights to develop and market any product candidate from our miniCEP290 program.

Under the license agreements for our product candidates, we generally 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 IC-500, also imposes specified diligence and milestone payment obligations on us. We may enter into acquisition or licensing agreements in the future that could impose similar obligations on us.

We are also party to research licenses with UMMS for rights to continue with the research and development of our miniABCA4 and miniUSH2A programs. The term of these research licenses is the same as the term for us to exercise our rights under option agreements pursuant to which UMMS granted us option rights to in-license certain patent applications covering these programs. If we fail to exercise our option rights or fail to agree to terms with UMMS for a license for further development and commercialization of the applicable program, we may lose our rights to continue with conducting research and development of that program.

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 ACP, DelSiTech's sustained release delivery technology, 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 $5.0 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, manufacture 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.

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 on 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 ACP 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 ACP are expected to expire in 2026. The U.S. patent rights covering methods of using ACP to treat GA are expected to expire in 2034. The European patent rights covering the composition of matter of ACP and methods of treating certain complement protein mediated disorders with ACP are expected to expire in 2025. The patents covering ACP may expire before the date by which we or a potential commercial partner would be able to commercialize ACP 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 ACP prior to the expiration of these patents, the remaining term of those patents may be shorter than we anticipate. If we are successful in developing a sustained release delivery technology for ACP, we may be able to obtain patent protection for ACP with the sustained release delivery technology beyond the current patent life for ACP; however, obtaining the additional patent protection from these efforts or other efforts to extend the patent life of ACP is not guaranteed. Although the patent rights under existing patent applications for IC-500 and our miniCEP290 program 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.

In 2022, the USPTO issued two patents with claims covering methods of using ACP to treat GA, which are method-of-treatment patents. Method-of-treatment patents are more difficult to enforce than composition-of-matter patents because of the risk of off-label sale or use of a drug for the patented method. The FDA does not prohibit physicians from prescribing an approved product for uses that are not described in the product's labeling. Although off-label use of a product 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 our product candidates would limit our ability to generate revenue from the sale of such product candidates, if approved for commercial sale. In addition, patent laws in Europe and some other jurisdictions generally make the issuance and enforcement of patents that cover methods of treatment of the human body difficult in those jurisdictions. Further, once the composition-of-matter patents relating to ACP in a particular jurisdiction, if any, expire, competitors will be able to make, offer and sell products containing the same drug substance as ACP in that jurisdiction so long as these competitors do not infringe any of our other patents covering ACP's composition of matter or method of use or manufacture, do not violate the terms of any marketing 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 ACP, 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 the portion of the 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 in-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.

We may not be successful in obtaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have rights to intellectual property, through licenses from third parties, to develop our product candidates. Because our programs may require the use of intellectual property or other proprietary rights held by third parties, the growth of our business may depend, in part, on our ability to acquire, in-license or use such intellectual property and proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes (and patents for such technology) or other intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Some of these institutions may provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate and our business, financial condition, results of operations and prospects could suffer.

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 or protect 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, patent laws in Europe and some other jurisdictions restrict 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, term, validity, 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. In addition, the issuance of any patents will depend on the existence of any prior art that comes to the patent examiner's attention during prosecution, sometimes through the actions of third parties, and whether our claimed invention meets the statutory criteria for being granted a patent in light of the prior art. 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, revised United States patent law in part by changing the standard for patent approval from a "first to invent" standard, which had existed before March 2013, to a "first to file" standard and developing a post-grant review system. 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. Trademark-related risks are increasing as we work to transition to a commercial-stage pharmaceutical company. 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 and we may not be able to obtain injunctive relief. 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 our collaborators, including our contract manufacturers and any commercial 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 are being filed at a rapid pace.

There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We or any collaborators 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 collaborators 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, use or sale. 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 manufacture or commercialization thereof, does not and will not infringe or otherwise violate any third party's intellectual property.

If we are or any of our collaborators 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, manufacturing and marketing our product candidates or products or to continue using a trademark. However, we or our collaborators 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 collaborators and could require us or them to make substantial licensing and royalty payments. We or our collaborators could be forced, including by court order, to cease using or 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 collaborators from making or 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 collaborators 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 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 some of the 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 IC-500 and the other 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 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. 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 become aware of such breach or may not be able to obtain adequate remedies. As we work on transitioning from a development-stage company to a company capable of commercializing a pharmaceutical product, we are hiring many new employees and engaging additional consultants and service providers, which increases the risk of disclosure or misuse of our proprietary information. 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 and Data Protection

We rely significantly upon our information technology systems and any failure, inadequacy, interruption or security lapse of those systems could harm our ability to operate our business effectively. Information technology risks have become more significant over time, including as a result of widespread remote working during the COVID-19 pandemic.

In the ordinary course of business, we collect, process and maintain personal and other sensitive data on our information technology networks. These data include our intellectual property and other proprietary or confidential information relating to our business as well as proprietary or confidential information of third parties including business collaborators. These data also include personal information relating to our clinical trial participants, employees and contractors, clinical investigators and other study staff and healthcare professionals. 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 an incident response plan and other standard operating procedures for responding to any cyber-security incidents, mandatory routine cyber-security training, including social engineering training, for our employees and consultants with access to our information technology systems, and engagement of a third-party vendor to regularly assess our informational technology systems and potential vulnerabilities.

Despite the implementation of security measures, our information technology systems 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 cyber and ransomware 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. In particular, there have been increasing number of cyber threats and attempts by foreign hackers targeted towards U.S. pharmaceutical and biotechnology companies and vendors they work with, including as a result of the ongoing military conflict in Ukraine.

As a result of the COVID-19 pandemic, we switched to remote and hybrid working since March 2020 and as a result, have increasingly relied upon teleconferencing and cloud-based means of communication and data storage. Many other companies have done the same. There have been numerous publicized attempts of bad actors attempting to intercept proprietary communications. We may be similarly susceptible to those kinds of threats.

Cyber-attacks have become more prevalent and much harder to detect and defend against. Our networks and storage applications may be subject to unauthorized access by hackers or breached due to human error, malfeasance or other system disruptions. We may not anticipate or immediately detect such incidents and the damage caused by such incidents. System failures, data breaches and any unauthorized access, use or disclosure of our information or data could compromise our intellectual property and expose sensitive business information; lead to unauthorized exposure of personal information of our clinical trial participants, our employees or contractors, our clinical investigators or other study staff, healthcare professionals or others we work with; and/or result in disruptions to our research and development activities and business operations, including potential product development, regulatory approval and commercialization delays.

In addition, cyber-attacks and the measures we implement to prevent, detect, and respond to them could cause us to incur significant remediation costs, including costs to recover or reproduce any compromised data, expose us to contractual damages and/or regulatory and other liability, require us to make certain breach notifications, and divert the attention of our management and key information technology resources. Any loss of preclinical data or clinical trial data could result in delays to our product development, marketing approval and commercialization efforts. We may not have adequate insurance coverage to provide compensation for any losses associated with such events and cybersecurity insurance is becoming more expensive. Any breach of security could harm our reputation and deter patients, clinical investigators, or other healthcare professionals and business collaborators from participating in our clinical trials or otherwise working with us.

We also rely significantly upon the information technology systems of our third-party service providers and any failure, inadequacy, interruption or security lapse of those systems could harm our ability to operate our business effectively. We have limited control and oversight over the information security systems and practices of third parties.

In the ordinary course of business, we rely on third parties, including clinical trial sites, CROs, CDMOs and other service providers, to collect, process and maintain personal and other sensitive data on their respective networks for our research and development activities and other business operations. These data include our intellectual property and other proprietary or confidential information relating to our business, as well as personal information relating to our clinical trial participants, employees and contractors, and clinical investigators, study staff and other healthcare professionals. The maintenance of our data by third parties does not absolve us of our responsibility for the security and integrity of this data.

We have limited control and oversight over the information security systems and practices of third parties. Those systems and practices vary widely in sophistication and robustness. We have limited personnel and resources to oversee the information security systems of third parties with whom we work.

Like our information security systems, those of our third-party service providers are vulnerable to compromise, damage, loss or exfiltration from cyber-attacks, computer viruses, unauthorized access and other causes. Our third-party service providers may not anticipate or immediately detect such incidents and the damage caused by such incidents or notify us in a timely or complete manner. System failures, data breaches and any unauthorized access, use or disclosure of our information or data maintained by our third-party service providers could lead to similar consequences for us as similar events involving our information technology systems, including compromise of our intellectual property or other sensitive personal or business information, disruptions and delays to our research and development activities and other operations, contractual and regulatory liability, data breach notifications, expenditure of significant costs and resources for remediation and harm to our reputation. Over the past few years, there has been an increasing number of and severity of cyber-attacks, especially ransomware attacks, against the information security systems of companies across the supply chain and other critical infrastructure service providers.

In September 2020, one of our vendors for the GATHER2 trial suffered a ransomware attack on several of its servers. While this vendor investigated and worked to mitigate the effects of the incident, we deployed a backup process for the work this vendor was performing for us. Although we do not believe this incident had a material impact on the GATHER2 trial or otherwise on our business or operations, similar kinds of incidents may occur in the future with this or our other vendors.

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 in line with our expectations, 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 personal information is rapidly evolving worldwide 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, and those frameworks may not be consistent. 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 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 of individuals in the European Union, 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. The GDPR also provides certain discretion to individual European member states, and many of them have enacted local legislation implementing the GDPR that differ from one another. The GDPR compliance framework is evolving as data protection authorities enforce applicable requirements and as European courts interpret the GDPR. We are aware that many other countries have enacted or are considering legislation similar to the GDPR.

Similar actions are either in place or under way in the United States. There are a broad variety of data protection laws that are applicable to our activities, and a wide range of enforcement agencies at both the state and federal levels with the authority to review our privacy and data security practices. The Federal Trade Commission and state Attorneys General have been increasingly active in reviewing companies' privacy and data security practices in relation to consumer information. New legislation and regulations are being considered, and in certain cases enacted, at both the state and federal levels. For example, the California Consumer Privacy Act, which went into effect on January 1, 2020, and its replacement, the California Privacy Rights Act, which became effective on January 1, 2023, are creating similar risks and obligations as those created by the GDPR. The New York SHIELD Act, which became fully effective in March 2020, imposes certain data security and data breach notification requirements on organizations that collect personal information of New York residents. Many other states

are considering similar legislation. A broad range of legislative measures are being introduced at the federal level. Accordingly, failure to comply with federal and state laws (both those currently in effect and future legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. We also may be subject to consumer class action litigation related to alleged noncompliance with these laws. Even if we are not determined to have violated these laws, responding to government investigations and/or consumer litigation in these areas typically requires the expenditure of significant resources and has the potential to generate negative publicity, which could harm our reputation and our business.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with these 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 on our behalf. 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, have resulted in certain changes to our business practices, such as additional consideration given to the GDPR and other relevant data protection laws in setting up clinical trial agreements and informed consent forms for our GATHER2 trial, and may require further changes to our business practices. As we set up our commercial infrastructure and practices, we would also need to be mindful of the Health Insurance Portability and Accountability Act, or HIPAA, and its rules and regulations governing protected health information. Any non-compliance by us or our employees, consultants or contractors with the GDPR, HIPAA or other applicable data protection laws 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 Employee Matters and Managing Our Operations

We are in the process of recruiting new personnel to prepare for the potential commercialization of ACP and to support our growth. We may experience difficulties in recruiting necessary and qualified personnel and in retaining key employees and consultants.

We are currently a development-stage company with a total of 163 full-time employees as of December 31, 2022. These employees support key areas of our business and operations, including commercial planning and operations, clinical development and clinical operations, regulatory affairs, drug safety, data management, biostatistics, medical affairs (including field personnel), scientific research, process and analytical development, drug substance and drug product manufacturing, quality control, materials and supply chain management, and quality assurance, as well as all of our general and administrative functions and public company infrastructure.

We remain highly dependent on Glenn P. Sblendorio, our chief executive officer, and Dr. Pravin U. Dugel, our 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. If any of those employees were to leave our company for any reason, 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. As we prepare for the potential commercialization of ACP, we have been and expect we will need to continue hiring additional personnel from this limited pool. We are starting to recruit and hire a field-based sales force. Hiring field-based personnel, and training and effectively deploying them, can be time consuming and expensive, and many other companies are competing with us for the field-based personnel whom we may seek to hire. If we experience any challenges or delays in the hiring and integration of necessary personnel, it could impede our ability to commercialize ACP and grow our business in line with our expectations.

In addition to our employees, we rely on consultants and advisors, including scientific, technical and clinical advisors, to assist us in formulating our research and development, manufacturing, commercialization and lifecycle management 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 specialized medical or clinical knowledge, 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 2015 our management concluded that we experienced a material weakness in internal controls that required us to restate the relevant financial statements and we took steps that year to address the deficiency and prevent similar deficiencies in the future. 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 will ensure that we maintain adequate controls over our financial reporting going forward and, accordingly, additional material weaknesses could occur or be identified. Any future material weaknesses or combination of deficiencies could materially and adversely affect our ability to provide timely and accurate financial information and investors' confidence in our internal controls and our company, which could cause our stock price to decline.

Risks Related to Legal and Compliance Matters

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, tracking of 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 possible requirement to implement a risk evaluation and mitigation strategy.

The FDA, the Federal Trade Commission and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the pre- and 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 preapproval promotion and off-label use and if we engage in inappropriate pre-approval promotion or if we do not market our products for their approved indications, we may be subject to enforcement action. Over the past few years, there has been increasing enforcement activity from the FDA targeting preapproval promotion. 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.

Non-compliance with European Union or other applicable requirements regarding safety monitoring or pharmacovigilance, and with any applicable requirements related to the development of products for the pediatric population, can also result in significant penalties.

Our and our potential commercialization partners' relationships with healthcare professionals, patients 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 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 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 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;
- 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 in connection with the delivery of or payment for benefits, items or services involving a healthcare benefit program;
- 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, and providing notifications of the breach of such information, by covered entities and certain business partners;

- 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, other healthcare providers 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 and may also require the licensing or listing of pharmaceutical sales representatives. 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 HIPAA and each other in significant ways, 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. These risks are becoming more important for our operations as ACP advances in clinical development and as we prepare for potential commercialization. We are working 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 are doing business or 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, and as a result, our relationships with those healthcare providers or third parties may be adversely affected and our business and reputation may suffer.

Current and future healthcare reform legislation may increase the difficulty and costs for us and any future collaborators to obtain reimbursement for any of our product candidates that may receive marketing approval and our ability to generate revenue will be materially impaired.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA. Other legislative changes have been proposed and adopted since the PPACA was enacted. The Budget Control Act of 2011, among other things, resulted in aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Further, with passage of the Inflation Reduction Act in August 2022, or the IRA, Congress extended the expansion of PPACA premium tax credits through 2025.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with the enactment of the Tax Cuts and Jobs Act of 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal

level of health insurance, became effective in 2019. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria and new payment methodologies that govern any of our approved products and/or the level of reimbursement physicians receive for administering any approved products we, or our collaborators, might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates for which we may obtain marketing approval and may affect our overall financial condition.

Current and future drug pricing legislative efforts may limit the prices for our products, if and when they are approved for marketing, which could materially impact our ability to generate revenues.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations included an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, was subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it would explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Medicare Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2026, by the Infrastructure Investment and Jobs Act.

On July 9, 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The executive order directs the Department of Health and Human Services, or HHS, to create a plan within 45 days to combat "excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging." On September 9, 2021, HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to: (a) make pharmaceutical prices more affordable and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; (b) improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the

Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at 2,000 a year. In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or "catastrophic period" of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period, must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co-insurance and co-payment costs, expanding eligibility for lower income subsidy plans, and price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

Accordingly, while it is currently unclear how the IRA will be effectuated, we cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. We expect that additional state and federal drug pricing measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for pharmaceutical products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Outside the United States, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the U.S., reimbursement and healthcare payment systems vary significantly by country and many countries have instituted price ceilings on specific products and therapies. In many countries, including those of the E.U. and the UK, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels, our business could be materially harmed.

Reporting and payment obligations under Medicare Part B, the Medicaid Drug Rebate Program and other governmental drug pricing programs are complex and may involve subjective decisions. Any failure to comply with those obligations could subject us to penalties and sanctions.

As a condition of reimbursement by various federal and state health insurance programs, pharmaceutical companies are required to calculate and report certain pricing information to federal and state agencies. The regulations governing the calculations, price reporting and payment obligations are complex and subject to interpretation by various government and regulatory agencies, as well as the courts. Reasonable assumptions have been made where there is lack of regulations or clear guidance and such assumptions involve subjective decisions and estimates. Pharmaceutical companies are required to report any revisions to calculations, price reporting and payment obligations previously reported or paid. Such revisions could result in liability to federal and state payers and also adversely impact reported financial results of operations in the period of such restatement. We expect that ACP, if approved for GA, would be reimbursed in large part by the "buy and bill" model under Medicare Part B, which requires that we report the average sale price, or ASP, for ACP, which will affect the level of reimbursement from Medicare. The determination of ASP can be complex and uncertain.

Uncertainty exists as new laws, regulations, judicial decisions, or new interpretations of existing laws or regulations related to calculations, price reporting or payments obligations, which increases the chances of a legal challenge, restatement or investigation. If a company becomes subject to investigations, restatements, or other inquiries concerning compliance with price reporting laws and regulations, it could be required to pay or be subject to additional penalties, sanctions or fines, which could have a material adverse effect on the business, financial condition and results of operations.

For example, the recently passed IRA has implications for programs such as Medicare Part D. Medicare Part D is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Individuals participating in a Medicare Part D prescription drug plan could experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or “catastrophic period” of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co-insurance and co-payment costs, expanding eligibility for lower income subsidy plans, and imposing price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

Further, state Medicaid programs may be slow to invoice pharmaceutical companies for calculated rebates resulting in a lag between the time a sale is recorded and the time the rebate is paid. This results in a company having to carry a liability on its consolidated balance sheets for the estimate of rebate claims expected for Medicaid patients. If actual claims are higher than current estimates, a company’s financial position and results of operations could be adversely affected.

In addition to retroactive rebates and the potential for 340B Program refunds, if a pharmaceutical company is found to have knowingly submitted any false price information related to the Medicaid Drug Rebate Program to CMS, it may be liable for civil monetary penalties. Such failure could also be grounds for CMS to terminate the Medicaid drug rebate agreement, pursuant to which companies participate in the Medicaid program. In the event that CMS terminates a rebate agreement, federal payments may not be available under government programs, including Medicare Part B, for covered outpatient drugs.

Additionally, if a pharmaceutical company overcharges the government in connection with the FSS program or Tricare Retail Pharmacy Program, whether due to a misstated federal ceiling price or otherwise, it is required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against a company under the FCA and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on a company’s business, financial condition and results of operations.

If we enter into a collaboration for commercialization of our product candidates outside the United States, our collaborators would be subject to similar requirements outside of the U.S. and thus the attendant risks and uncertainties. If our collaborators suffer material and adverse effects from such risks and uncertainties, our rights and benefits for our licensed products could be negatively impacted, which could have a material and adverse impact on our revenues.

Inadequate funding for the FDA, the SEC and other government agencies, including from government shutdowns, or other disruptions to these agencies’ operations, could prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes, which has caused average review times to fluctuate in recent years. Disruptions at the FDA and other agencies may slow the time for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last decade the U.S. government has

shutdown several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough employees and stop critical activities. It is possible government shutdowns may occur during the current Congress. 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.

Separately, in response to the COVID-19 pandemic, a number of companies in 2021 announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Following a period of false starts and temporary suspensions due to the Omicron variant, the FDA resumed domestic inspections in February 2022 and indicated that it would conduct foreign inspections beginning in April 2022 on a prioritized basis. However, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required, due to the ongoing COVID-19 pandemic and travel restrictions. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. In addition, many state licensing agencies underwent reductions in staff and office operations in wake of the COVID-19 pandemic and as a result, are taking longer to review and approve pharmaceutical licensing applications. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

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 have relationships with certain officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations, including a number of public hospitals that are our clinical trial sites. 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 or governmental programs, 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. Our operations at our laboratories and with our contracted manufacturing services 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 or our contractors' 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 injuries at work, 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. We expect the Biden Administration to pass additional such laws and regulations. Some of those laws and regulations may govern the health and safety measures that employers must implement to protect their workers from the COVID-19 virus.

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. There is also increasing focus from regulators and self-regulatory organizations on the environmental impact of operations and additional obligation on companies to make disclosures relating to them.

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, including as a result of short selling by institutional and retail investors. 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, for example the increase in the trading of our common stock following our announcement of topline data from our GATHER2 trial;
- the timing and results of regulatory interactions and review for our product candidates;
- the success of products or technologies that compete with our product candidates, including results of clinical trials of product candidates of our competitors and of regulatory review of those product candidates, including the increase in the trading of our common stock around Apellis's announcement on February 17, 2023 of the FDA's approval of its product pegcetacoplan for treatment of GA secondary to AMD;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- the level of expenses related to any of our product candidates or development programs;
- variations in our financial results or those of companies that are perceived to be similar to us;
- the recruitment or departure of key personnel;
- the results of our efforts to in-license or acquire the rights to other product candidates and technologies for the treatment of retinal diseases, including additional sustained release delivery technologies for ACP;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- relevant scientific and medical developments;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions, such as those caused by the COVID-19 pandemic or the ongoing military conflict in Ukraine or potentially high inflation rates;
- political, social, 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 were named as defendants in a purported class action lawsuit and a related shareholder derivative action following our announcement in December 2016 of the initial, topline results from the first two of our Phase 3 Fovista trials for the treatment of wet AMD, which caused our stock price to decline significantly. See Note 12 to the Financial Statements. 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, and cause additional volatility in the price of our common stock.

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. If the holders of a significant number of shares our common stock 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 common stock at a discount pursuant to our Employee Stock Purchase Plan.

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 common stock. 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 significant 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, including potential environmental, social and governance (ESG) reporting.

As a public company, we incur and will continue to incur significant legal, accounting and other expenses. 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. 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.

On March 21, 2022, the Securities and Exchange Commission proposed new rules relating to the disclosure of climate-related risks and disclosures. The SEC is currently reviewing comments to the proposed rule and a final rule is forthcoming. We are currently assessing the rule and its potential impact on our operations. To the extent this rule is finalized as proposed, we expect we would need to devote significant time and incur increased costs preparing for the disclosures required by this rule. In addition to the SEC's climate-related rule, many public companies are choosing or being required to report on their ESG goals, practices and risks, which could also require our management's time and increase our costs.

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 our Loan Agreement and any future debt

agreements that we may enter into may preclude us from paying dividends without the lender's consent or at all. 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

We lease properties in Parsippany, New Jersey and Cranbury, New Jersey, all of which are used for office space and/or storage of IT equipment. We also have several lab benches for use in Worcester, Massachusetts, which we license from the University of Massachusetts and where we have several employees doing laboratory research and other preclinical development work.

Item 3. Legal Proceedings

Descriptions of legal proceedings are set forth in "Note 12-Commitments and Contingencies" in the notes to the financial statements filed with this Annual Report on Form 10-K.

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, 2023, there were approximately 96 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

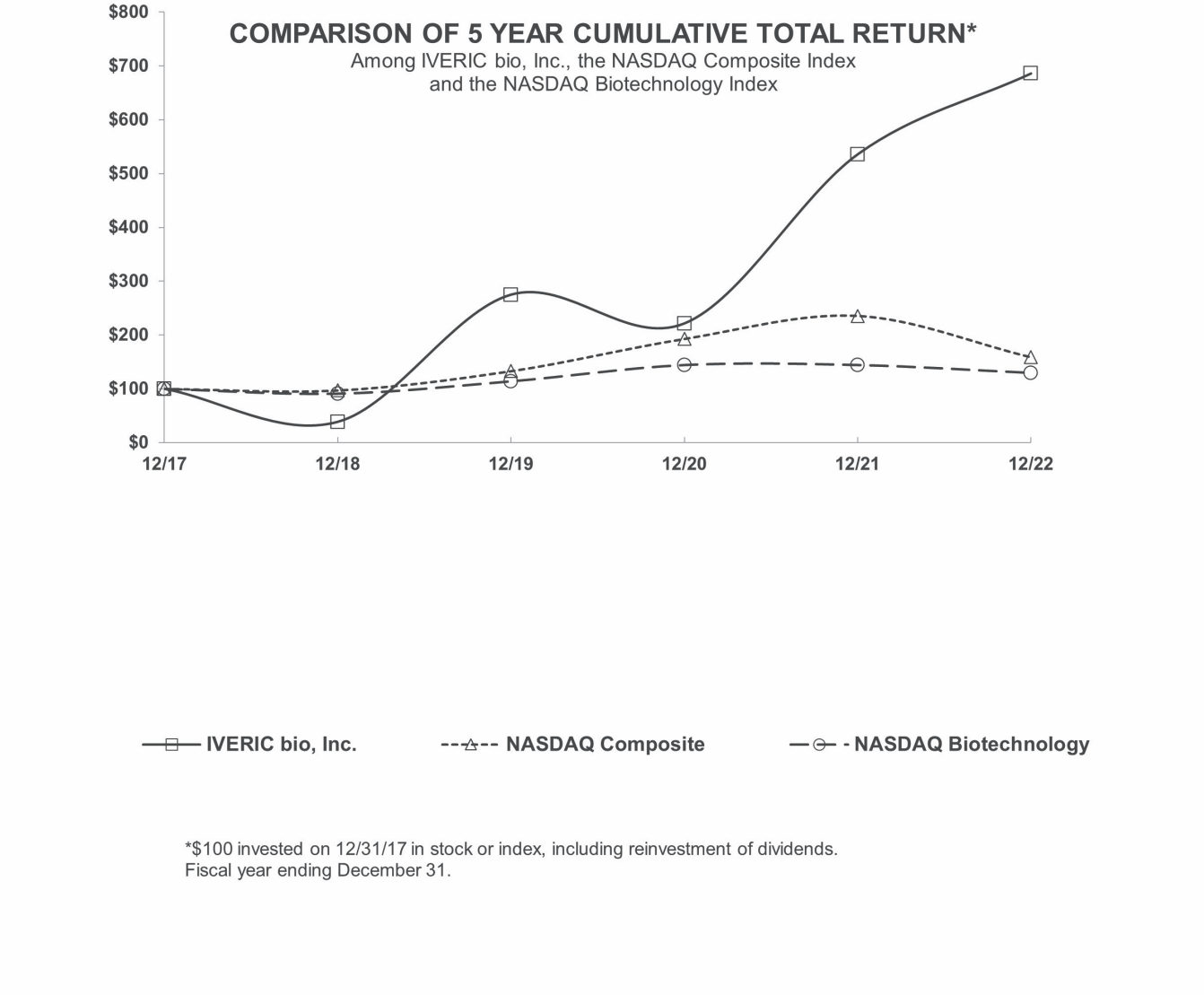
We did not sell any of our equity securities or any options, warrants or rights to purchase our equity securities during the period covered by this Annual Report on Form 10-K that were not registered under the Securities Act and that have not otherwise been described in a Current Report on Form 8-K or a Quarterly Report on Form 10-Q.

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, 2017 and ending on December 31, 2022, to that of the total return for the NASDAQ Composite Index and the NASDAQ Biotechnology Index, assuming an investment of $100 on December 31, 2017. 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 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.



Item 6. Reserved

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

The following discussion and analysis is meant to provide material information relevant to an assessment of the financial condition and results of operations of our company, including an evaluation of the amounts and certainty of cash flows from operations and from outside sources, so as to allow investors to better view our company from management's perspective. This discussion and analysis 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 treatments for retinal diseases with significant unmet medical needs. We are committed to having a positive impact on patients' lives by delivering high-quality, safe and effective treatments designed to address debilitating retinal diseases, including earlier stages of age-related macular degeneration, or AMD.

Our lead asset is our clinical stage product candidate ACP, which is also referred to as ACP or Zimura®, a complement C5 inhibitor. We are currently targeting the following diseases with ACP:

- Geographic Atrophy, or 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;
- intermediate AMD, which is an earlier stage of AMD; and
- autosomal recessive Stargardt disease, or STGD1, which is an orphan inherited condition characterized by progressive damage to the central portion of the retina, or the macula, and other retinal tissue, leading to loss of vision.

In October 2019, we announced positive 12-month data for GATHER1, our first Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD. In GATHER1, 286 patients were randomized to receive various doses of ACP, including ACP 2 mg, or sham control. We observed a 27.7% (p-value = 0.0063) reduction in the mean rate of growth (slope) estimated based on GA area between the ACP 2 mg group and the corresponding sham control group over 12 months, when performing the primary analysis, and a 35.4% (p-value = 0.0050) reduction in the mean rate of growth (slope) estimated based on GA area between the two groups over 12 months, when performing the supportive analysis. These results are based on an analysis of the primary efficacy endpoint required by the U.S. Food and Drug Administration, or FDA, in accordance with our Special Protocol Assessment, or the SPA, which we describe further below. We analyzed the endpoint by using the square root transformation of the GA area, which we refer to as the primary analysis, and we analyzed the endpoint by using the observed GA area (without square root transformation), which we refer to as the supportive analysis. In GATHER1, through month 12, we did not observe any events of endophthalmitis or ischemic optic neuropathy events, and only one case of intraocular inflammation, which was mild and transient and reported as related to the injection procedure. The incidence of choroidal neovascularization, or CNV, in the study eye through month 12 was 6 patients (9.0%) in the ACP 2 mg group and 3 patients (2.7%) in the corresponding sham control group.

In June 2020, we started enrolling patients in GATHER2, our second Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD. In July 2021, we received a written agreement from the FDA under the SPA for the overall design of GATHER2. The SPA is a procedure by which the FDA provides a clinical trial sponsor with an official evaluation and written guidance on the design of a proposed protocol intended to form the basis for a new drug application, or NDA. In connection with our SPA, the FDA recommended, and we accepted, modifying the primary efficacy endpoint for the GATHER2 trial from the mean rate of change in GA area over 12 months measured by fundus autofluorescence, or FAF, at three timepoints: baseline, month 6 and month 12, to the mean rate of growth (slope) estimated based on GA area measured by FAF in at least three timepoints: baseline, month 6 and month 12.

In September 2022, we announced positive 12-month top-line data for GATHER2. In GATHER2, 448 patients were randomized on a 1:1 basis to receive ACP 2 mg or sham control over the first 12 months of the trial. At 12 months, we measured the primary efficacy endpoint in accordance with the SPA. In GATHER2, we observed a 14.3% (p-value = 0.0064) reduction in the mean rate of growth (slope) in GA area between the two groups at 12 months with the primary analysis, and a 17.7% (p-value = 0.0039) reduction in the mean rate of growth (slope) in GA area between the two groups at 12 months with the supportive analysis. We did not observe any events of endophthalmitis, intraocular inflammation events, events of vasculitis or ischemic optic neuropathy events through month 12, and the incidence of CNV in the study eye through month 12 was 15 patients (6.7%) in the ACP 2 mg group and 9 patients (4.1%) in the sham control group.

We believe that with the statistically significant results from our GATHER1 and GATHER2 trials and the safety profile of ACP to date, we have sufficient data from two independent, adequate and well-controlled pivotal clinical trials of ACP in GA secondary to AMD to support an application for marketing approval. In November 2022, the FDA granted breakthrough therapy designation to ACP for the treatment of GA secondary to AMD. In December 2022, we completed the rolling submission of our NDA to the FDA for marketing approval of ACP for the treatment of GA secondary to AMD. In February 2023, the FDA accepted our NDA for filing and granted priority review with a Prescription Drug User Fee Act, or PDUFA, target action date of August 19, 2023.

In addition to ACP, we are developing our preclinical product candidate IC-500, a High temperature requirement A serine peptidase 1 protein, or HtrA1, inhibitor, for GA secondary to AMD and potentially other age-related retinal diseases. Based on current timelines and subject to successful preclinical development and current good manufacturing practices, or cGMP, manufacturing, we expect to submit an investigational new drug application, or IND, to the FDA for IC-500 during the first half of 2024.

Our portfolio also includes several ongoing gene therapy research programs, each of which uses adeno-associated virus, or AAV, for gene delivery. These AAV mediated gene therapy programs are targeting the following orphan inherited retinal diseases, or IRDs:

- Leber Congenital Amaurosis type 10, or LCA10, which is characterized by severe bilateral loss of vision at or soon after birth;
- STGD1; and
- IRDs associated with mutations in the USH2A gene, which include Usher syndrome type 2A, or Usher 2A, and USH2A-associated non-syndromic autosomal recessive retinitis pigmentosa.

Recent Impact of COVID-19 and other Macroeconomic Events

The COVID-19 pandemic and other macro-economic events, such as the military action taken by Russia against Ukraine, and governmental responses to those events have affected the world economy in various ways, including causing delays and challenges to the global supply chain and the work and operations of many manufacturers and service providers. We rely heavily on third-party contract manufacturing organizations, contract research organizations and other vendors to support our clinical trials, manufacturing activities and other business operations. We describe below some of the recent impacts of these macro-economic events on our business and operations.

Over the past three years, the pharmaceutical industry and the contract manufacturing organizations and suppliers supporting the industry have been impacted by global supply chain disruptions in wake of the COVID-19 pandemic. For example, the new manufacturer we are working with as a second source of supply for ACP drug substance has experienced issues with procuring a number of raw materials due to supply chain interruptions, which caused several delays to our manufacturing timelines with this manufacturer. To date, we have not experienced any drug product supply issues impacting our GATHER2 and STAR clinical trials or the OLE study and we do not believe our overall timelines for ACP have been materially impacted as a result of supply chain issues affecting our contract manufacturers. The impact of the COVID-19 pandemic and future variants and subvariants on our operations remains uncertain and we are continuing to monitor the situation closely.

We do not believe that the COVID-19 pandemic, and our actions in response and the costs of those actions, have had a material impact on our financial position, results of operations, or cash flows for the year ended December 31, 2022. For further information on actual and potential impacts to us as a result of the COVID-19 pandemic, see the Risk Factors contained in this Annual Report on Form 10-K.

Business Development and Financing Activities

As we prepare for the potential marketing approval and potential commercial launch of ACP, progress our research and development programs and evaluate our overall strategic priorities, we continue to pursue selective business development and financing opportunities that advance us toward our strategic goals. We have been focused on pursuing potential sustained release delivery technologies for ACP, such as DelSiTech's silica-based sustained release technology, for which we entered into the DelSiTech License Agreement. We plan to continue to evaluate, on a selective and targeted basis, opportunities to obtain rights to additional product candidates and technologies for retinal diseases, with a focus on additional sustained release delivery technologies for ACP. In addition, we plan to explore potential collaboration opportunities for the future development and potential commercialization of ACP in one or more territories outside the United States.

Opus Asset Purchase Agreement

As part of our previously stated strategy to seek a licensee for IC-100 and IC-200, in December 2022, IVERIC bio Gene Therapy LLC, or the Iveric Subsidiary, our wholly owned subsidiary, entered into an asset purchase agreement with Opus Genetics Inc., or Opus, or the Opus APA, pursuant to which Opus acquired all rights, title and interests in and to Iveric Subsidiary's assets primarily related to IC-100 and IC-200, including Iveric Subsidiary's exclusive license agreements with the University of Florida Research Foundation, Incorporated, or UFRF, and the Trustees of the University of Pennsylvania, or Penn, for both product candidates and certain related sponsored research agreements.

In accordance with the terms of the Opus APA, Iveric Subsidiary received (i) an upfront payment in the amount of $500,000 and (ii) 2,632,720 shares of the Series Seed Preferred Stock of Opus, pursuant to a stock issuance agreement, or the Opus SPA, that the parties entered into currently with the Opus APA, resulting in Iveric Subsidiary's ownership of a high single-digit percentage of the outstanding capital stock of Opus on a fully diluted basis. The Opus APA and the Opus SPA provide for Opus to issue additional shares of capital stock that will maintain Iveric Subsidiary's ownership at a mid to high single-digit percentage of the fully diluted outstanding capital stock of Opus through Opus's next round of financing in which it raises a specified minimum amount of gross proceeds. Iveric Subsidiary is also eligible to receive (i) contingent development and regulatory milestone payments of up to $12.8 million and (ii) additional sales milestone payments of up to $98.9 million from Opus. Further, Iveric Subsidiary will receive, on a country-by-country and product-by-product basis, an earn-out of a low single-digit percentage on net sales of IC-100 and IC-200.

The Opus APA also contains customary representations, warranties, covenants and indemnification obligations made by Iveric Subsidiary and Opus.

Opus will be responsible for all further research, development, and commercialization of IC-100 and IC-200 globally and replaced Iveric Subsidiary as the exclusive licensee under the license agreements with UFRF and Penn. However, under certain circumstances, Iveric Subsidiary may have certain rights with respect to the potential future commercialization of IC-100 and/or IC-200.

The sale of IC-100 and IC-200 pursuant to the Opus APA closed in December 2022.

2022 Term Loan Facility

In July 2022, we executed a Loan and Security Agreement, or the Loan Agreement, with Hercules Capital, Inc., or Hercules, and Silicon Valley Bank, or SVB, for a $250.0 million term loan facility, or the 2022 Term Loan Facility. The 2022 Term Loan Facility has tranched availability as follows:

- $50.0 million which was fully funded at closing.
- $50.0 million which we borrowed in December 2022
- $25.0 million available at our option through September 30, 2023, which we plan to borrow during 2023.
- $75.0 million available at our option through the earlier of (a) September 30, 2024, or (b) 90 days following FDA approval of the use of ACP for GA, subject to our achieving such approval; and
- $50.0 million available with lender approval.

Upon achievement of the relevant conditions specified in the Loan Agreement, future borrowings are at our election and are in $5.0 million increments. The outstanding principal balance of the 2022 Term Loan Facility bears interest at a floating interest rate per annum equal to the greater of either (i) (x) the lesser of the Wall Street Journal prime rate and 6.25% plus (y) 4.00% or (ii) 8.75%. Interest rate per annum is capped at 10.25%. With the exception of the first $50.0 million tranche funded at closing, each of the tranches may be drawn in $5.0 million increments at our election. The 2022 Term Loan Facility includes a 42 month interest only period and is extendable up to five years upon meeting certain conditions.

For more detailed information about the 2022 Term Loan Facility and our follow-on public offering that we closed in December 2022, please see the Liquidity and Capital Resources section of this Management's Discussion and Analysis of Financial Condition and Results of Operations. Although we believe we have sufficient financial resources to launch ACP for GA in the United States, if approved based on our current business plan, we expect to continue to pursue capital raising transactions when they are available on terms favorable to us and if the opportunity advances our strategic goals.

Financial Operations Overview

Revenue

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

product candidates result in regulatory approval or if we enter into collaboration agreements with third parties, we may generate revenue from product sales or from such third parties.

Our ability to become and remain profitable depends on our ability to generate revenues 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.

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 research programs. Our research and development expenses consist of:

- external research and development expenses incurred under arrangements with third parties, such as 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, *Research and Development.* 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, 2022, 2021 and 2020:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
ACP	$ 76,014	$ 53,208	$ 28,366
IC-500: HtrA1	3,257	2,070	1,442
IC-100: RHO-adRP	336	1,211	6,874
IC-200: BEST1	(1,440)	2,974	7,718
Other gene therapy	115	26	932
Fovista	1	(7)	(741)
Personnel-related	26,344	18,821	13,426
Share-based compensation	11,865	6,522	4,166
Other	520	243	601
	$ 117,012	$ 85,068	$ 62,784

As we continue our ongoing clinical trials and manufacturing activities for ACP, we expect our research and development expenses for ACP to increase. We expect our research and development expenses for IC-500 to increase as we continue preclinical development. We expect our research and development expenses for our miniCEP290 program and other gene therapy research programs to remain largely unchanged as we continue those programs. Our research and development expenses may increase if we in-license or acquire any new product candidates or technologies, including potential sustained release delivery technologies for ACP or any promising product candidates from our minigene programs, or if we commence any new development programs.

We expect the development of our product candidates will continue for at least the next several years. At this time, we cannot reasonably estimate that 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 ACP for indications outside of GA or for any of our other 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 are conducting the GATHER2 trial, which is a Phase 3 clinical trial evaluating ACP for GA, with the expectation that data collected from this trial, together with other available data, will be sufficient to seek and obtain 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, conduct additional clinical trials or nonclinical studies of ACP 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 development of ACP 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, commercial planning and operations, legal, finance, business development, human resources, investor relations and information technology functions. We expect that our general and administrative expenses to continue to increase as we continue to hire personnel for our commercial organization, including sales, marketing, access and reimbursement and operations personnel, and we continue to build our capabilities for the commercial launch of ACP, if approved. 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, cash equivalents and available-for-sale securities in money market funds, U.S. Treasury securities, investment-grade corporate debt securities, asset-backed securities and debt instruments issued by foreign governments, 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 and share-based compensation 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 CROs, CDMOs and other vendors in connection with research and development and manufacturing activities.

We base our expenses related to 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.

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.

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.

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, 2022, 2021 and 2020:

	Years ended December 31,		
	2022	2021	2020
Expected common stock price volatility	84%	114%	118%
Risk-free interest rate	1.38%-4.29%	0.31%-1.22%	0.22%-1.34%
Expected term of options (years)	4.6	5.2	4.6
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 $26.7 million, $11.2 million and $8.3 million for the years ended December 31, 2022, 2021, and 2020, respectively. As of December 31, 2022, we had $103.4 million of total unrecognized share-based compensation expense, which we expect to recognize over a weighted-average remaining vesting period of approximately 3.2 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, 2022, 2021 and 2020, we allocated share-based compensation as follows:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
Research and development	$ 11,865	$ 6,522	$ 4,166
General and administrative	14,811	4,723	4,157
Total	$ 26,676	$ 11,245	$ 8,323

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. In March 2020, February 2021, September 2021, December 2021, May 2022 and February 2023, our board of directors amended the Inducement Plan to reserve an additional 1,000,000 shares of our common stock, an additional 600,000 shares of our common stock, an additional 1,000,000 shares of our common stock, an additional 1,000,000 shares of our common stock, an additional 1,000,000 shares of our common stock, and an additional 2,000,000 shares of our common stock, respectively, for issuance under the plan. The Inducement Plan permits us to, subject to the approval of each grant by the compensation and talent strategy 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. As of December 31, 2022, we had approximately 791,000 shares available for issuance under the Inducement Plan.

Results of Operations

	Years ended December 31,		
	2022	2021	2020
		(in thousands)	
Statements of Operations Data:			
Operating expenses:			
Research and development	$ 117,012	$ 85,068	$ 62,784
General and administrative	72,894	29,689	25,952
Total operating expenses	189,906	114,757	88,736
Loss from operations	(189,906)	(114,757)	(88,736)
Interest income, net	2,264	245	500
Gain on sale of IC100 & IC200	2,369	—	—
Other income (expense), net	62	(10)	(6)
Loss before income tax benefit	(185,211)	(114,522)	(88,242)
Income tax benefit	—	—	3,695
Net loss	$ (185,211)	$ (114,522)	$ (84,547)

Research and Development Expenses

Our research and development expenses were $117.0 million for the year ended December 31, 2022, an increase of $31.9 million compared to $85.1 million for the year ended December 31, 2021. The increase in research and development expenses for the year ended December 31, 2022, was primarily due to a $22.8 million increase in costs associated with ACP, a $12.9 million increase in personnel costs, including share-based compensation associated with additional research and development staffing, and a $1.2 million increase in costs associated with IC-500. The increase in research and development expenses were partially offset by a $4.4 million decrease in costs associated with IC-200 and a $0.9 million decrease in costs associated with IC-100. The increased costs for ACP were primarily due to the continued progress of our GATHER2 trial and increased manufacturing activities for ACP. The decreased costs for IC-100 and IC-200 primarily reflect decreased manufacturing and preclinical development activities.

General and Administrative Expenses

Our general and administrative expenses were $72.9 million for the year ended December 31, 2022, an increase of $43.2 million, compared to $29.7 million for the year ended December 31, 2021. The increase in general and administrative expenses was primarily due to an increase in costs associated with preparing for the commercialization of ACP, including personnel costs and share-based compensation.

Interest Income, net

Interest income, net for the year ended December 31, 2022, was $2.3 million compared to interest income of $0.2 million for the year ended December 31, 2021. The increase in interest income earned during the year ended December 31, 2022 was primarily due to the increases in our cash, cash equivalents and marketable securities balance and interest rate yields during the year. The increase in interest income was partially offset by the interest expense related to our 2022 Term Loan Facility.

Gain on sale of IC-100 and IC-200

During December 2022, we recognized a gain of $2.4 million for the sale of IC-100 and IC-200.

Income Tax Benefit

We recorded no benefit from income taxes for the years ended December 31, 2022, and December 31, 2021.

Liquidity and Capital Resources

Sources of Liquidity

Since inception, we have financed our operations primarily through private placements of our common stock and preferred stock, venture debt borrowings, funds received under the Novo Holdings A/S Agreement, our initial public offering, which we closed in September 2013, funds we received under a prior agreement with Novartis Pharma AG related to the licensing and commercialization of Fovista, funds we received in connection with our acquisition of Inception 4, Inc., or Inception 4, in October 2018, our follow-on public offerings, which we closed in February 2014, December 2019, June 2020, July 2021, October 2021 and December 2022, including the sale of pre-funded warrants in December 2019 and June 2020, and the 2022 Term Loan Facility.

In July 2022, we entered into a Loan and Security Agreement, or the Loan Agreement, with Hercules and SVB for the 2022 Term Loan Facility, which consists of several tranches of potential financing in an aggregate principal amount of up to $250.0 million. The first tranche consisted of a term loan advance in the amount of $50.0 million funded upon execution of the Loan Agreement on July 26, 2022. An aggregate of $150.0 million may be drawn at our option, in three separate tranches, subject to our achievement of specified performance milestones relating to development and regulatory events for ACP, as described below in "—Contractual Obligations and Commitments". We achieved the first performance milestone in September 2022 and borrowed the full $50.0 million tranche in the fourth quarter of 2022. An additional $50.0 million is available subject to the approval of the facility lenders' investment committees in their discretion. Loans outstanding under facility bear interest at a floating interest rate per annum equal to the greater of either (i) (x) the lesser of the Wall Street Journal prime rate and 6.25% plus (y) 4.00% or (ii) 8.75%, capped at 10.25%. The facility matures in August 2027 and has an initial interest-only payment period of 42 months, which may be extended to up to 60 months upon the satisfaction of certain conditions.

We currently have an effective universal shelf registration statement on Form S-3, or the March 2021 Shelf Registration, on file with the SEC registering for sale from time to time up to $300.0 million of common stock, preferred stock, debt securities, depositary shares, subscription rights, warrants and/or units in one or more registered offerings, of which $100.0 million may be offered, issued and sold under an "at-the-market" Sales Agreement, or the ATM Agreement, with Cowen and Company, LLC. We also have an automatically effective shelf registration statement on Form S-3, or the October 2021 Shelf Registration, pursuant to which we may offer and sell an indeterminate amount of shares of common stock, preferred stock, debt securities, depositary shares, subscription rights, warrants and/or units in one or more registered offerings.

In July 2021, we closed an underwritten public offering in which we sold 13,397,500 shares of our common stock under the March 2021 Shelf Registration, which included the exercise in full of the underwriters' option to purchase an additional 1,747,500 shares of our common stock, at a price to the public of $8.60 per share and at a price to the underwriters of $8.084 per share. The net proceeds from the public offering, after deducting underwriting discounts and commissions and other offering expenses payable by us totaling approximately $7.4 million, were approximately $107.8 million.

In October 2021, we closed an underwritten public offering in which we sold 10,350,000 shares of our common stock under the October 2021 Shelf Registration, which included the exercise in full of the underwriters' option to purchase an additional 1,350,000 shares of our common stock, at a price to the public of $16.75 per share and at a price to the underwriters of $15.745 per share. The net proceeds from the public offering, after deducting underwriting discounts and commissions and other offering expenses payable by us totaling approximately $10.8 million, were approximately $162.6 million.

In December 2022, we completed an underwritten public offering in which we sold 15,352,500 shares of our common stock under the October 2021 Shelf Registration, which included the exercise in full of the underwriters' option to purchase 2,002,500 shares of our common stock, at a price to the public of $22.50 per share and at a price to the underwriters of $21.150 per share. The net proceeds from the December 2022 public offering, after deducting underwriting discounts and commissions and other expenses payable by us totaling approximately $21.1 million, were approximately $324.3 million.

We have not yet issued and sold any shares of our common stock under the ATM Agreement.

Cash Flows

As of December 31, 2022, we had cash, cash equivalents and available-for-sale securities totaling $646.8 million and $96.6 million of debt. We primarily invest our cash, cash equivalents and available-for-sale securities in money market funds, U.S. Treasury securities, certain investment-grade corporate debt securities, asset-backed securities and debt instruments issued by foreign governments.

The following table shows a summary of our cash flows for the years ended December 31, 2022, 2021 and 2020:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
Net cash (used in) provided by:			
Operating Activities	$ (163,771)	$ (98,559)	$ (66,097)
Investing Activities	(50,277)	21,298	(143,810)
Financing Activities	428,905	272,335	150,581
Net change in cash and cash equivalents	$ 214,857	$ 195,074	$ (59,326)

Cash Flows from Operating Activities

Net cash used in operating activities was $163.8 million and $98.6 million for the years ended December 31, 2022, and 2021, respectively, which primarily related to net cash used to fund our ACP clinical trials and manufacturing activities and to support the preclinical development activities of IC-500.

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 used in investing activities was $50.3 million for the year ended December 31, 2022, which primarily related to the purchases of available-for-sale securities. Net cash provided by investing activities for the year ended December 31, 2021, was $21.3 million and primarily related to the maturities of available-for-sale securities.

Cash Flows from Financing Activities

Net cash provided by financing activities for the year ended December 31, 2022, was $428.9 million and relates primarily to cash received from our public offering of our common stock in December 2022 as well as amounts borrowed under the 2022 Term Loan Facility with Hercules and SVB in July 2022 and December 2022. Net cash provided by financing activities for the year ended December 31, 2021, was $272.3 million and relates primarily to cash received from our public offering of our common stock and concurrent private placement in June 2020.

Funding Requirements

ACP is in clinical development, IC-500 is in preclinical development, and we are exploring multiple sustained release delivery technologies for ACP and advancing multiple gene therapy research programs. We expect our research and development expenses to increase as we pursue these programs as currently planned. We could incur additional research and development expenses if we modify or further expand the scope of our clinical trials, such as our initiation of the OLE study for ACP in GA secondary to AMD, our preclinical development programs or our gene therapy research programs, or if we in-license or acquire, and undertake development of, additional product candidates and technologies, including additional sustained release delivery technologies for ACP and any promising product candidates that emerge from our gene therapy research programs. We could also incur additional research and development expenses if, for example, we are required by the FDA, the EMA or regulatory authorities in other jurisdictions, or if we otherwise decide, to perform clinical trials and/or nonclinical or other studies in addition to those we currently expect to conduct. If we experience delays or disruptions to our research and development programs, including delays in patient enrollment or issues with patient retention or patients missing scheduled visits and treatments, if we experience issues with our preclinical development programs, such as unfavorable toxicology or other preclinical data, if we experience issues with the manufacture and supply of product candidates, including issues with process development or manufacturing scale-up activities, whether such delays or disruptions are due to the COVID-19 pandemic or other reasons, we could incur additional and unexpected expenses as a result of such delays or disruptions and our business and financial results may be materially impacted. Furthermore, if we successfully develop and expect to 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 have started incurring these expenses as we prepare for the potential commercialization of ACP. We are party to agreements with Archemix with respect to ACP, DelSiTech with respect to formulations of ACP with DelSiTech's silica-based sustained release delivery technology, the former equityholders of Inception 4 with respect to IC-500, and UMass with respect to any potential product candidates from our miniCEP290 program, in each case, that impose significant milestone payment obligations on us if we or a potential collaborator achieves specified clinical, regulatory and commercial milestones with respect to these product candidates, as well as certain royalties on net sales with respect to formulations of ACP with DelSiTech's silica-based sustained release delivery

technology 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:

- build our commercial operations and sales, marketing and distribution capabilities for ACP;
- expand our outsourced manufacturing capabilities for ACP and IC-500;
- continue the development of ACP in GA, STGD1 and potentially other indications;
- seek marketing approval for ACP and any other product candidates that successfully complete clinical trials;
- in-license or acquire the rights to, and pursue the development of, other product candidates or technologies for retinal diseases, such as sustained release delivery technologies for ACP;
- continue the development of IC-500 and pursue our gene therapy research programs;
- maintain, expand and protect our intellectual property portfolio;
- hire additional commercial, medical affairs, clinical, regulatory, pharmacovigilance, manufacturing, quality control, quality assurance and scientific personnel; and
- expand our general and administrative functions to support our future growth.

As of December 31, 2022, we had approximately $646.8 million in cash, cash equivalents and available-for-sale securities. We estimate that our cash, cash equivalents, available for sale securities and committed loan facilities will be sufficient to fund our planned capital expenditure requirements, debt service obligations and operating expenses through at least the next twelve months. These estimates do not include any potential new borrowings under the 2022 Term Loan Facility with Hercules and SVB beyond the $25.0 million that we plan to borrow during 2023 based on our achievement of the performance milestone related to the FDA's acceptance of our NDA for filing.

Although we believe we have sufficient financial resources to launch ACP for GA secondary to AMD in the United States, if approved based on our expectations, we may need additional funding to continue to commercialize ACP for GA, if approved. We expect we will require substantial, additional funding in order to complete the activities necessary to develop and commercialize ACP for other indications, a sustained release delivery technology for ACP or any of our other product candidates. 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 ACP for any other indication, a sustained release delivery technology for ACP or for any of our other product candidates.

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

- the costs, timing and outcome of regulatory filings and reviews of our product candidates, including regulatory review of our filed NDA and the planned submission of MAAs for ACP in GA secondary to AMD;
- the timing, scope and costs of establishing a commercial infrastructure for potential commercialization of ACP, including the hiring and deployment of a sales force and the establishment of sales, marketing and distribution capabilities;
- the scope, progress, costs and results of process development, manufacturing scale-up and validation activities, analytical method development and qualification, and stability studies associated with ACP and our other product candidates;
- the scope, progress, costs and results of our current and future ACP clinical programs and any further development we may undertake;
- our ability to establish collaborations on favorable terms, if at all, if we choose to do so, including a potential collaboration for the further development and potential commercialization of ACP in one or more territories outside the United States;
- the extent to which we in-license or acquire rights to, and undertake research or development of, additional product candidates or technologies, including sustained release delivery technologies for ACP;

- the extent of our debt service obligations and our ability, if desired, to refinance any of our existing debt on terms that are more favorable to us;
- the scope, progress, costs and results of our efforts to develop IC-500, including activities to establish manufacturing capabilities and other preclinical development activities to enable us to submit an IND for this product candidate;
- the scope, progress, costs and results from our gene therapy 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 timing and extent of delays or disruptions to our research and development programs as a result of the COVID-19 pandemic and other macro-economic events;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending intellectual property-related claims; 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.

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. For example, the COVID-19 pandemic and other macro-economic events, such as the current high levels of inflation, and governmental responses to those events have caused volatility and uncertainty in the financial markets as well as additional volatility in the price of our stock, which may result in prospective investors being less likely to invest new capital. 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 successful in raising approximately $324.3 million in net proceeds in an underwritten public offering of our common stock in December 2022, 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, Nasdaq listing rules 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 or reduce our future commercialization efforts, or delay, reduce or terminate the development of one or more of our product candidates.

We may require additional funding beyond what we currently expect due to unforeseen or other reasons. Our costs may exceed our expectations if the timeline for potential commercial launch of ACP is accelerated, if we need to establish commercial infrastructure or capabilities, including hiring additional personnel or conducting additional disease-state awareness activities, to a greater extent than we have planned, or if we choose not to or are unable to find a collaborator for commercialization of ACP in one or more territories outside the United States. Our costs may also exceed our expectations if we experience an issue with manufacturing, such as issues with process development, scale-up and validation, or establishing and qualifying second source suppliers and ensuring adequate inventory for our expected needs, including potential launch of ACP; if we experience an issue in our clinical trials, such as issues with patient enrollment, the retention of enrolled patients, enrolled patients maintaining scheduled visits and receiving scheduled treatments, or the availability of drug supply; if we experience an issue in our preclinical development programs, such as unfavorable toxicology or other preclinical data; or if we modify or further expand the scope of our clinical trials, preclinical development programs or gene therapy 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 trials or nonclinical or other studies in addition to those we currently expect to conduct. For example, we believe that the data from the GATHER2 trial, together with other available data, are sufficient to support applications for marketing approval in the United States, the European Union and the United Kingdom. We may subsequently decide to, or be required by regulatory authorities to, conduct additional clinical trials or nonclinical studies of ACP in order to seek or maintain marketing approval or qualify for reimbursement approval. In addition, the COVID-19 pandemic and other macroeconomic events may result in disruptions to the progress of the GATHER2 or STAR trials or the OLE study, including slowing patient enrollment in STAR or causing enrolled patients in either trial to miss their scheduled visits or drop out in greater numbers than we expect, or disruptions to our other research and development programs, which could cause us to continue to expend our cash resources while not progressing our research and development programs as expeditiously as we would have had the pandemic not occurred or persisted. 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 obtain regulatory approval and launch ACP in GA secondary to AMD. Our future commercial revenues, if any, will be derived from product sales, which may not be available or become substantial for a period of time following launch. In addition, if approved, our products 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.

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 paid Archemix an aggregate of $9.0 million in fees based on our achievement of specified clinical milestone events under the C5 License Agreement, including two milestone payments of $1.0 million and $6.0 million triggered by the positive 12-month data from, and by completion of, the GATHER1 trial, which we paid in March 2020 and October 2020, respectively.

Under the C5 License Agreement, for each anti-C5 aptamer product that we may develop under the agreement, including ACP, we are obligated to make additional payments to Archemix of up to an aggregate of $50.5 million if we achieve specified development, clinical and regulatory milestones, with $24.5 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—ACP - Archemix C5 License Agreement" in Part I, Item 1 of this Annual Report on Form 10-K.

Inception 4 Merger Agreement

In October 2018, we and Inception 4 entered into the Inception 4 Merger Agreement, pursuant to which we acquired IC-500 and our other HtrA1 inhibitors through a merger transaction.

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—IC-500 - Inception 4 Merger Agreement" in Part I, Item 1 of this Annual Report on Form 10-K.

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.

Contractual Obligations and Commitments

Our purchase obligations include agreements and contracts that give the supplier recourse to us for cancellation or nonperformance under the contract or contain terms that would subject us to liquidated damages. Such agreements and contracts may, for example, be related to direct materials and certain of our manufacturing and supply agreements.

In addition we may be required, under the agreements under which we acquired rights to ACP, IC-500 and our miniCEP290 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. For a description of these agreements see Note 12, *Commitments and Contingencies.*

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 2022 annual meeting of stockholders, as filed with the SEC on March 30, 2022.

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.

For a description of other contractual obligations, see Note 10, *Loan and Security Agreement*, and Note 11, *Operating Leases*, to the Consolidated Financial Statements.

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

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and available-for-sale securities of $646.8 million as of December 31, 2022, consisting of cash and investments in money market funds, U.S. Treasury securities, U.S. Government Agency securities, corporate debt securities, asset-based securities and supranational 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, CDMOs and certain other vendors to perform services outside the United States. 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, 2022, 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 (PCAOB ID: 42), appear on pages F-4 through F-31 of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. 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, 2022, 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, 2022. 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, 2022, our internal control over financial reporting was effective.

The effectiveness of the Company's internal control over financial reporting as of December 31, 2022, 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 occurred in our internal control over financial reporting (as defined in Rules 13a-15(d) and 15d-15(d) under the Exchange Act) during the quarter ended December 31, 2022, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting. Further, we have not experienced any material impact to our internal controls over financial reporting as a result of our employees working remotely due to the COVID-19 pandemic.

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, 2022, 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, 2022, 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, 2022 and 2021, and the consolidated statements of operations, comprehensive loss, changes in stockholders' equity and cash flows for each of the three years in the period ended December 31, 2022 and the related notes and our report dated March 1, 2023 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
March 1, 2023

Item 9B. Other Information

None.

Item 9C. Foreign Jurisdictions that Prevent Inspections

Not applicable.

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 2023 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 2023 Annual Meeting of Shareholders and is incorporated in this Annual Report on Form 10-K by reference.

Code of Business Conduct and Ethics

We have adopted a code of business conduct and ethics, or the Code of Ethics, which 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. We are currently updating the Code of Ethics to reflect our potential growth to a commercial stage company, and plan to continue training our directors, officers and employees on the Code of Ethics annually.

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 2023 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 2023 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 2023 Annual Meeting of Shareholders and, other than the information required by Item 402(v) of Regulation S-K, 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 2023 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 2023 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 2023 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)
2.2	^	Asset Purchase Agreement by and between Opus Genetics Inc. and IVERIC bio Gene Therapy LLC dated December 23, 2022
2.3	^	Stock Issuance Agreement by and between Opus Genetics Inc. and IVERIC bio Gene Therapy LLC dated December 23, 2022
3.1		Restated Certificate of Incorporation of the Registrant, as amended on April 16, 2019 (incorporated by reference to Exhibit 3.1 of the Registrant's Annual Report on Form 10-K filed on March 4, 2021)
3.2		Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.4 of the Registrant's Registration Statement on Form S-1, as amended (File No. 333-190643))
4.1		Description of Registered Securities of the Registrant (incorporated by reference to Exhibit 4.1 of the Registrant's Annual Report on Form 10-K filed on February 27, 2020)
4.2		Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.2 of the Registrant's Annual Report on Form 10-K filed on February 27, 2020)
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 + Amendment No. 1 to 2016 Employee Stock Purchase Plan

10.11 + 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)

10.12 + Amendment No. 1 to 2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on May 7, 2020)

10.13 + Amendment No. 2 to 2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 10.12 of the Registrant's Annual Report on Form 10-K filed on March 4, 2021)

10.14 + Amendment No. 3 to 2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on November 9, 2021)

10.15 + Amendment No. 4 to 2019 Inducement Stock Incentive Plan of the Registrant (incorporated by reference to Exhibit 10.14 of the Registrant's Annual Report on Form 10-K filed on February 24, 2022)

10.16 + Amendment No. 5 to 2019 Inducement Plan of the Registrant (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on July 26, 2022)

10.17 + Amendment No. 6 to 2019 Inducement Plan of the Registrant

10.18 + 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)

10.19 + 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)

10.20 † 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))

10.21 ^ Exclusive License Agreement between the Registrant and DelSiTech Ltd., dated June 30, 2022 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on July 26, 2022)

10.22 ^ 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)

10.23 ^ Loan and Security Agreement between the Registrant, IVERIC bio Gene Therapy LLC, Orion Ophthalmology LLC, each of the Registrant's other subsidiaries from time to time party thereto as a borrower, Hercules Capital, Inc., Silicon Valley Bank, and the several banks and other financial institutions or entities from time to time parties thereto, and Hercules Capital Inc., in its capacity as administrative agent and collateral agent for itself and the lenders, dated July 26, 2022 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on July 26, 2022)

10.24 + 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)

10.25 + 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)

10.26 + 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)

10.27 + Letter Agreement between the Registrant and Glenn P. Sblendorio, dated November 3, 2021 (incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q filed on November 9, 2021)

10.28 + Letter Agreement between the Registrant and David F. Carroll, dated April 24, 2017 (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q filed on August 2, 2017)

10.29 + Letter Agreement between the Registrant and David F. Carroll, dated December 11, 2019 (incorporated by reference to Exhibit 10.34 of the Registrant's Annual Report on Form 10-K filed on February 27, 2020)

10.30	+	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)
10.31	+	Letter Agreement between the Registrant and Keith Westby, dated December 11, 2019 (incorporated by reference to Exhibit 10.36 of the Registrant's Annual Report on Form 10-K filed on February 27, 2020)
10.32	+	Offer Letter between the Registrant and Pravin U. Dugel dated March 11, 2020 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020)
10.33	+	Letter Agreement between the Registrant and Pravin U. Dugel dated March 11, 2020 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020)
10.34	+	Offer Letter between the Registrant and Christopher Simms dated June 16, 2021 (incorporated by reference to Exhibit 10.33 of the Registrant's Annual Report on Form 10-K filed on February 24, 2022)
10.35	+	Letter Agreement between the Registrant and Christopher Simms dated June 16, 2021 (incorporated by reference to Exhibit 10.34 of the Registrant's Annual Report on Form 10-K filed on February 24, 2022)
10.36	+	Offer Letter between the Registrant and Tony Gibney dated November 19, 2021 (incorporated by reference to Exhibit 10.35 of the Registrant's Annual Report on Form 10-K filed on February 24, 2022)
10.37	+	Letter Agreement between the Registrant and Tony Gibney dated November 10, 2021 (incorporated by reference to Exhibit 10.36 of the Registrant's Annual Report on Form 10-K filed on February 24, 2022)
10.38	+	Retirement and Consulting Agreement between the Registrant and David Guyer dated April 5, 2021 (incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K filed on April 5, 2021)
10.39	+	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)
10.40	+	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)
10.41	+	Amendment No. 1 to Non-Employee Director Compensation Policy of the Registrant (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q filed on November 3, 2020)
10.42	+	Amendment No. 2 to Non-Employee Director Compensation Policy of the Registrant (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on May 5, 2021)
10.43	+	Amendment No. 3 to Non-Employee Director Compensation Policy of the Registrant (incorporated by reference to Exhibit 99.1 of the Registrant's Current Report on Form 8-K filed on January 11, 2022)
10.44	+	Amendment No. 4 to Non-Employee Director Compensation Policy (incorporated by Reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q filed on May 4, 2022)
14.1		Code of Business Conduct and Ethics of the Registrant (incorporated by reference to Exhibit 14.1 of the Registrant's Annual Report on Form 10-K filed February 27, 2020)
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: March 1, 2023

IVERIC bio, Inc.

By: /s/ GLENN P. SBLENDORIO

Glenn P. Sblendorio
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	Chief Executive Officer and Director (principal executive officer)	March 1, 2023
/s/ DAVID F. CARROLL David F. Carroll	Senior Vice President and Chief Financial Officer (principal financial and accounting officer)	March 1, 2023
/s/ ADRIENNE L. GRAVES Adrienne L. Graves, Ph.D.	Chairman of the Board of Directors	March 1, 2023
/s/ MARK BLUMENKRANZ Mark Blumenkranz, M.D.	Director	March 1, 2023
/s/ AXEL BOLTE Axel Bolte	Director	March 1, 2023
/s/ PRAVIN U. DUGEL Pravin U. Dugel, M.D.	Director and President	March 1, 2023
/s/ JANE P. HENDERSON Jane P. Henderson	Director	March 1, 2023
/s/ CHRISTINE ANN MILLER Christine Ann Miller	Director	March 1, 2023
/s/ CALVIN W. ROBERTS Calvin W. Roberts, M.D.	Director	March 1, 2023

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, 2022 and 2021, the related consolidated statements of operations, comprehensive loss, changes in stockholders' equity and cash flows for each of the three years in the period ended December 31, 2022 and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, 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, 2022, 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 March 1, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the 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.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued research and development costs

Description of the Matter

During 2022, the Company incurred $117 million of research and development expenses and accrued $12 million for research and development expenses as of December 31, 2022. As described in Note 2 to the Financial Statements, service agreements with third party service providers including contract research organizations ("CROs") and contract development and manufacturing organizations ("CMOs") comprise a significant component of the Company's research and development activities. The timing and the amount of payments required under each individual arrangement are often different from the pattern of costs actually incurred. The Company accrues the cost of the services with these third-party organizations based on the extent of activities completed by vendors and measured by internal project managers.

Auditing management's accounting for accrued contract research and development expenses is especially challenging because amounts owed to third parties are accrued based upon estimates of the proportion of work completed for each of the individual clinical trial and manufacturing activities in accordance with the unique terms and conditions of each respective CRO and CMO agreement. Estimating the proportion of work completed requires the application of judgments by management that are dependent on inputs, such as the number of sites activated, the number of patients enrolled

and the number of patient visits, obtained from clinical personnel and third-party service providers and compiled from multiple sources.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design, and tested the operating effectiveness of internal controls over the completeness and valuation of accrued research and development expenses, including controls over the judgments made by management and the data obtained from clinical personnel and third-party service providers.

To test the research and development accrual, our audit procedures included, among others, testing the accuracy and completeness of the underlying data used in the estimates and evaluating the estimated proportion of work completed for each of the individual clinical trial and manufacturing activities used by management to estimate the recorded accruals. We inspected the contracts and any amendments to the contracts with third-party service providers, assessed the progress of clinical trials and other research and development projects with the Company's research and development personnel that oversee the clinical trials, and obtained information directly from third parties, which included the third parties' estimates of costs incurred to date. We also inspected subsequent invoices received from third parties.

/s/ Ernst & Young LLP

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

Iselin, New Jersey
March 1, 2023

IVERIC bio, Inc.

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2022	December 31, 2021
Assets		
Current assets		
Cash and cash equivalents	$ 476,304	$ 261,447
Available for sale securities	170,531	120,302
Prepaid expenses and other current assets	15,991	5,739
Total current assets	662,826	387,488
Property and equipment, net	946	348
Right-of-use assets, net	1,182	1,522
Other assets	1,869	—
Total assets	$ 666,823	$ 389,358
Liabilities and Stockholders' Equity		
Current liabilities		
Accrued research and development expenses	$ 11,555	$ 14,403
Accounts payable and accrued expenses	22,843	12,856
Lease liability, current	1,189	952
Total current liabilities	35,587	28,211
Lease liability, non-current	11	619
Debt, non-current	96,568	—
Total liabilities	132,166	28,830
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, 136,639,687 and 115,277,012 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	137	115
Additional paid-in capital	1,399,555	1,040,098
Accumulated deficit	(864,806)	(679,595)
Accumulated other comprehensive income	(229)	(90)
Total stockholders' equity	534,657	360,528
Total liabilities and stockholders' equity	$ 666,823	$ 389,358

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,		
	2022	**2021**	**2020**
Operating expenses:			
Research and development	$ 117,012	$ 85,068	$ 62,784
General and administrative	72,894	29,689	25,952
Total operating expenses	189,906	114,757	88,736
Loss from operations	(189,906)	(114,757)	(88,736)
Interest income, net	2,264	245	500
Gain on sale of IC100 & IC200	2,369	—	—
Other income (expense), net	62	(10)	(6)
Loss before income tax benefit	(185,211)	(114,522)	(88,242)
Income tax benefit	—	—	3,695
Net loss	$ (185,211)	$ (114,522)	$ (84,547)
Net loss per common share:			
Basic and diluted	$ (1.53)	$ (1.12)	$ (1.14)
Weighted average common shares outstanding:			
Basic and diluted	121,037	101,866	74,185

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

IVERIC bio, Inc.

Consolidated Statements of Comprehensive Loss

(in thousands)

	Years ended December 31,		
	2022	**2021**	**2020**
Net loss	$ (185,211)	$ (114,522)	$ (84,547)
Other comprehensive income			
Unrealized (loss) gain on available-for-sale securities, net of tax	(139)	(93)	3
Other comprehensive (loss) income	(139)	(93)	3
Comprehensive loss	$ (185,350)	$ (114,615)	$ (84,544)

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

IVERIC bio, Inc.

Consolidated Statements of Changes in 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, 2019	—	$ —	49,627	$ 50	$ 597,679	$ (480,526)	$ —	$ 117,203
Issuance of common stock and pre-funded warrants through underwritten offering, net of issuance costs	—	—	28,504	28	116,855	—	—	116,883
Issuance of common stock in connection with private offering	—	—	8,649	9	33,228	—	—	33,237
Issuance of common stock under employee stock compensation plans	—	—	841	1	460	—	—	461
Share-based compensation	—	—	—	—	8,323	—	—	8,323
Issuance of common stock under the exercise of pre-funded warrants	—	—	2,500	2	(2)	—	—	—
Net loss	—	—	—	—	—	(84,547)	—	(84,547)
Unrealized gain on available for sale securities, net of tax	—	—	—	—	—	—	3	3
Balance at December 31, 2020	—	$ —	90,121	$ 90	$ 756,543	$ (565,073)	$ 3	$ 191,563
Issuance of common stock through underwritten offering, net of issuance costs	—	—	23,748	24	270,295	—	—	270,319
Issuance of common stock under employee stock compensation plans	—	—	1,408	1	2,015	—	—	2,016
Share-based compensation	—	—	—	—	11,245	—	—	11,245
Net loss	—	—	—	—	—	(114,522)	—	(114,522)
Unrealized gain on available for sale securities, net of tax	—	—	—	—	—	—	(93)	(93)
Balance at December 31, 2021	—	$ —	115,277	$ 115	$ 1,040,098	$ (679,595)	$ (90)	$ 360,528
Issuance of common stock through underwritten offering, net of issuance costs	—	—	15,353	15	324,275	—	—	324,290
Issuance of common stock under employee stock compensation plans	—	—	6,010	7	8,506	—	—	8,513
Share-based compensation	—	—	—	—	26,676	—	—	26,676
Net loss	—	—	—	—	—	(185,211)	—	(185,211)
Unrealized loss on available for sale securities, net of tax	—	—	—	—	—	—	(139)	(139)
Balance at December 31, 2022	—	$ —	136,640	$ 137	$ 1,399,555	$ (864,806)	$ (229)	$ 534,657

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,		
	2022	**2021**	**2020**
Operating Activities			
Net loss	$ (185,211)	$ (114,522)	$ (84,547)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities:			
Depreciation	138	39	143
Amortization of debt issuance costs	466	—	—
Amortization of premium and discounts on investment securities	(623)	1,182	462
Proceeds from sale of IC100 & IC 200	(500)	—	—
Share-based compensation	26,676	11,245	8,323
Change in working capital	(31)	54	—
Changes in operating assets and liabilities:			
Income tax receivable	—	1,765	—
Prepaid expense and other assets	(12,121)	(943)	(2,742)
Accrued interest receivable	296	438	(323)
Accrued research and development expenses	(2,848)	2,119	5,424
Accounts payable and accrued expenses	9,987	64	7,163
Net cash used in operating activities	(163,771)	(98,559)	(66,097)
Investing Activities			
Purchase of marketable securities	(231,040)	(142,821)	(143,810)
Maturities of marketable securities	180,999	164,480	—
Purchase of property and equipment	(736)	(361)	—
Proceeds from sale of assets	500	—	—
Net cash provided by (used in) investing activities	(50,277)	21,298	(143,810)
Financing Activities			
Proceeds from follow-on public offering, net	324,290	270,319	116,883
Proceeds from issuance of common stock related to private placement	—	—	33,237
Proceeds from employee stock plan purchases and stock option exercises	8,513	2,016	461
Proceeds from term loan	100,000	—	—
Payment of term loan issuance costs	(3,898)	—	—
Net cash provided by financing activities	428,905	272,335	150,581
Net increase (decrease) in cash and cash equivalents	214,857	195,074	(59,326)
Cash and cash equivalents			
Beginning of period	261,447	66,373	125,699
End of period	$ 476,304	$ 261,447	$ 66,373
Supplemental disclosure of cash paid			
Interest expense paid in cash	1,760	—	—
Income taxes received, net	$ —	$ (1,765)	$ (3,327)
Supplemental disclosures of non-cash information related to investing activities			
Change in unrealized gain (loss) on available for sale securities, net of tax	$ (139)	$ (93)	$ 3
Operating right-of-use assets obtained in exchange for lease obligations	$ 953	$ 2,086	$ 166
Preferred stock received for the sale of IC100 & IC200	$ 1,869	$ —	$ —

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

1. Business

Description of Business and Organization

IVERIC bio, Inc. (the "Company") is a science-driven biopharmaceutical company focused on the discovery and development of novel treatments for retinal diseases with significant unmet medical needs. The Company is committed to having a positive impact on patients' lives by delivering high-quality, safe and effective treatments designed to address debilitating retinal diseases, including earlier stages of age-related macular degeneration ("AMD").

The Company's lead asset is its clinical stage product candidate avacincaptad pegol (also referred to as ACP or Zimura), a complement C5 inhibitor. It is currently targeting the following diseases with ACP:

- Geographic Atrophy ("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;
- intermediate AMD, which is an earlier stage of AMD; and
- autosomal recessive Stargardt disease ("STGD1"), which is an orphan inherited condition characterized by progressive damage to the central portion of the retina (the "macula") and other retinal tissue, leading to loss of vision.

In October 2019, the Company announced positive 12-month data for GATHER1, its first Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD. In GATHER1, 286 patients were randomized to receive various doses of ACP, including ACP 2 mg, or sham control. The Company observed a 27.7% (p-value = 0.0063) reduction in the mean rate of growth (slope) estimated based on GA area between the ACP 2 mg group and the corresponding sham control group over 12 months, when performing the primary analysis, and a 35.4% (p-value = 0.0050) reduction in the mean rate of growth (slope) estimated based on GA area between the two groups over 12 months, when performing the supportive analysis. These results are based on a post-hoc analysis of the GATHER1 data using the U.S. Food and Drug Administration ("FDA") preferred primary efficacy endpoint analysis from the Company's Special Protocol Assessment ("SPA"), which is described further below. The Company analyzed the endpoint by using the square root transformation of the GA area, which it refers to as the primary analysis, and the Company analyzed the endpoint by using the observed GA area (without square root transformation), which it refers to as the supportive analysis. In GATHER1, through month 12, the Company did not observe any events of endophthalmitis or ischemic optic neuropathy events, and only one case of intraocular inflammation, which was mild and transient and reported as related to the injection procedure. The incidence of choroidal neovascularization ("CNV") in the study eye through month 12 was 6 patients (9.0%) in the ACP 2 mg group and 3 patients (2.7%) in the corresponding sham control group.

In June 2020, the Company started enrolling patients in GATHER2, its second Phase 3 clinical trial evaluating ACP for the treatment of GA secondary to AMD. In July 2021, the Company received a written agreement from the FDA under the SPA for the overall design of GATHER2. The SPA is a procedure by which the FDA provides a clinical trial sponsor with an official evaluation and written guidance on the design of a proposed protocol intended to form the basis for a new drug application ("NDA"). In connection with our SPA, the FDA recommended, and the Company accepted, modifying the primary efficacy endpoint for the GATHER2 trial from the mean rate of change in GA area over 12 months measured by fundus autofluorescence ("FAF") at three timepoints: baseline, month 6 and month 12, to the mean rate of growth (slope) estimated based on GA area measured by FAF in at least three timepoints: baseline, month 6 and month 12.

In September 2022, the Company announced positive 12-month top-line data for GATHER2. In GATHER2, 448 patients were randomized on a 1:1 basis to receive ACP 2 mg or sham control over the first 12 months of the trial. At 12 months, the Company measured the primary efficacy endpoint in accordance with the SPA. In GATHER2, the Company observed a 14.3% (p-value = 0.0064) reduction in the mean rate of growth (slope) in GA area between the two groups at 12 months with the primary analysis, and a 17.7% (p-value = 0.0039) reduction in the mean rate of growth (slope) in GA area between the two groups at 12 months with the supportive analysis. The Company did not observe any events of endophthalmitis, intraocular inflammation events, events of vasculitis or ischemic optic neuropathy events through month 12, and the incidence of choroidal neovascularization ("CNV") in the study eye through month 12 was 15 patients (6.7%) in the ACP 2 mg group and 9 patients (4.1%) in the sham control group.

The Company believes that with the statistically significant results from its GATHER1 and GATHER2 trials and the safety profile of ACP to date, it has sufficient data from two independent, adequate and well-controlled pivotal clinical trials of

1. Business (Continued)

ACP in GA secondary to AMD to support an application for marketing approval. In November 2022, ACP became the first investigational drug product to receive breakthrough therapy designation from the FDA for the treatment of GA secondary to AMD. In December 2022, the Company completed the rolling submission of its new drug application ("NDA") to the FDA for marketing approval of ACP for the treatment of GA secondary to AMD. In February 2023, the FDA accepted its NDA for filing and granted priority review with a Prescription Drug User Fee Act ("PDUFA") target action date of August 19, 2023.

In addition to ACP, the Company is developing its preclinical product candidate IC-500, a High temperature requirement A serine peptidase 1 protein ("HtrA1") inhibitor, for GA secondary to AMD and potentially other age-related retinal diseases. Based on current timelines and subject to successful preclinical development and current good manufacturing practices manufacturing, the Company expects to submit an investigational new drug application to the FDA for IC-500 during the first half of 2024.

The Company's portfolio also includes several ongoing gene therapy research programs, each of which uses adeno-associated virus ("AAV") for gene delivery. These AAV mediated gene therapy programs are targeting the following orphan inherited retinal diseases ("IRDs"):

- Leber Congenital Amaurosis type 10 ("LCA10"), which is characterized by severe bilateral loss of vision at or soon after birth;
- STGD1; and
- IRDs associated with mutations in the USH2A gene, which include Usher syndrome type 2A, and USH2A-associated non-syndromic 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 and accounting for share-based compensation. Actual results could differ from those estimates.

Cash and Cash Equivalents and Available-for-Sale Securities

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 Company's Consolidated Balance Sheets for cash and cash equivalents are valued at cost, which approximates their fair value.

2. Summary of Significant Accounting Policies (Continued)

The Company considers debt securities with original maturities of greater than 90 days to be available-for-sale securities. Available-for-sale securities with original maturities of greater than one year are recorded as non-current assets. Available-for-sale securities are recorded at fair value and unrealized gains and losses are recorded within other comprehensive income.

On a quarterly basis, the Company reviews the status of each security in an unrealized loss position, to evaluate the existence of potential credit losses. The Company first considers whether it intends to sell, or if it is more likely than not that the Company will be required to sell the security before recovery of its amortized cost basis. If either of the criteria regarding intent or requirement to sell is met, the security's amortized cost basis is written down to fair value through income. For securities that do not meet this criteria, the Company considers a number of factors to determine if the decline in fair value has resulted from credit losses or other factors, including but not limited to: (1) the extent of the decline; (2) changes to the rating of the security by a rating agency; (3) any adverse conditions specific to the security; and (4) other market conditions that may affect the fair value of the security. If this assessment indicates that a credit loss exists and the present value of cash flows expected to be collected is less than the amortized cost basis, an allowance for credit losses is required for the credit loss. Any impairment that has not been recorded through an allowance for credit losses is recognized in other comprehensive income.

As of December 31, 2022, the Company had cash, cash equivalents and available-for-sale securities of approximately $646.8 million. The Company believes that its cash, cash equivalents and available-for-sale securities as of December 31, 2022, 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.

Concentration of Credit Risk

The Company's financial instruments that are exposed to concentration of credit risk consist primarily of cash, cash equivalents and available-for-sale securities. The Company maintains its cash in bank accounts, the balances of which generally exceed federally insured limits. The Company maintains its cash equivalents and available-for-sale securities in investments in money market funds, in U.S. Treasury securities, U.S. Government Agency securities, investment-grade corporate debt securities, asset-backed securities and debt instruments issued by foreign governments with original maturities of 90 days or less.

The Company believes it is not exposed to significant credit risk on its cash, cash equivalents and available-for-sale securities.

Concentration of Suppliers

The Company historically relied upon a single third-party manufacturer to provide the drug substance for ACP on a purchase order basis. The Company also historically relied upon a single third-party manufacturer to provide fill/finish services for clinical supplies of ACP. The Company has engaged one additional third-party manufacturer to provide drug substance for ACP and one additional third-party manufacturer to provide fill/finish services for clinical supplies of ACP. In addition, the Company currently relies upon a single third-party supplier to supply on a purchase order basis the polyethylene glycol starting material used to manufacture ACP. 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 ACP. The Company currently relies upon a single third-party contract manufacturer to provide the drug substance for IC-500 for preclinical toxicology studies and early-stage clinical trials and a single third-party contract manufacturer to conduct fill/finish services for IC-500 drug product. 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, insolvency or the impact of COVID-19, 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.

Equity Investments

The Company holds investments in equity securities without a readily determinable fair value. Equity investments without a readily determinable fair value are recognized at fair value and are adjusted for observable price changes, or when qualitative assessments indicate that impairment exists, which is recorded in other income (loss).

2. Summary of Significant Accounting Policies (Continued)

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. The carrying amount of the Company's term loan approximates fair value due to the variable interest rate nature of the debt.

Accounting Standards Codification, or 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 cash, cash equivalents and available-for-sale financial assets. The market approach uses prices and other relevant information generated by market transactions involving identical or comparable assets. 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.

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.

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.

Leases

The Company determines if an arrangement contains a lease at inception. For arrangements where the Company is the lessee, it recognizes a right-of-use ("ROU") asset and operating lease liability on the Company's Consolidated Balance Sheet. ROU 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

2. Summary of Significant Accounting Policies (Continued)

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. ROU assets include 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.

Property and Equipment

Property and equipment, which consists mainly of clinical equipment, laboratory equipment, computers, software, other office equipment, automobiles 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, development, and preclinical and clinical testing of the Company's product candidates and costs associated with its gene therapy research programs. The Company's research and development expenses consist of:

- external research and development expenses incurred under arrangements with third parties, such as contract research organizations ("CROs") and contract development and manufacturing organizations ("CDMOs") 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.

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, non-employee directors and certain other individuals, 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. For grants containing a market condition, the Company estimated the fair value using a Monte Carlo simulation model which takes into consideration different stock price paths. The Company

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

2. Summary of Significant Accounting Policies (Continued)

recognizes compensation expense for the market award on a straight-line basis over the derived service period. Compensation expense is recognized for market awards, so long as the requisite service is provided.

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.

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 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, 2022, 2021 and 2020:

	Years ended December 31,		
	2022	2021	2020
Expected common stock price volatility	84%	114%	118%
Risk-free interest rate	1.38%-4.29%	0.31%-1.22%	0.22%-1.34%
Expected term of options (years)	4.6	5.2	4.6
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,		
	2022	2021	2020
Research and development	$ 11,865	$ 6,522	$ 4,166
General and administrative	14,811	4,723	4,157
Total	$ 26,676	$ 11,245	$ 8,323

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2. Summary of Significant Accounting Policies (Continued)

Recently Adopted Accounting Pronouncements

The Company has evaluated recent accounting pronouncements through the date the financial statements were issued and filed with the SEC and believes that there are none that will have a material impact on the Company's financial statements.

3. Common Stock

December 2022 Follow-on Public Offering

In December 2022, the Company completed an underwritten public offering in which the Company sold 15,352,500 shares of its common stock, which included the exercise in full of the underwriters' option to purchase 2,002,500 shares of the Company's common stock, at a price to the public of $22.50 per share and at a price to the underwriters of $21.15 per share.

The net proceeds from the December 2022 public offering, after deducting underwriting discounts and commissions and other expenses payable by the Company totaling approximately $21.1 million, were approximately $324.3 million.

October 2021 Follow-on Public Offering

In October 2021, the Company completed an underwritten public offering in which the Company sold 10,350,000 shares of its common stock, which included the exercise in full of the underwriters' option to purchase 1,350,000 shares of the Company's common stock, at a price to the public of $16.75 per share and at a price to the underwriters of $15.745 per share.

The net proceeds from the October 2021 public offering, after deducting underwriting discounts and commissions and other expenses payable by the Company totaling approximately $10.8 million, were approximately $162.6 million.

July 2021 Follow-on Public Offering

In July 2021, the Company completed an underwritten public offering in which the Company sold 13,397,500 shares of its common stock, which included the exercise in full of the underwriters' option to purchase an additional 1,747,500 shares of the Company's common stock, at a price to the public of $8.60 per share and at a price to the underwriters of $8.084 per share.

The net proceeds from the July 2021 public offering, after deducting underwriting discounts and commissions and other expenses payable by the Company totaling approximately $7.4 million, were approximately $107.8 million.

June 2020 Follow-on Public Offering and Private Placement

In June 2020, the Company closed an underwritten public offering in which it sold 28,503,220 shares of its common stock, which includes the exercise in full of the underwriters' option to purchase additional shares of its common stock, at a price to the public of $4.10 per share, and at a price to the underwriters of $3.854 per share. The Company also sold to certain investors in lieu of common stock, pre-funded warrants to purchase 1,914,280 shares of its common stock at a price to the public of $4.099 per share underlying each pre-funded warrant, and at a price to the underwriters of $3.853 per share underlying each pre-funded warrant. The pre-funded warrants are immediately exercisable with certain restrictions and do not expire.

Concurrently with the June 2020 public offering, the Company completed a private placement exempt from the registration requirements of the Securities Act of 1933, as amended (the "Securities Act"), in which it sold 8,649,453 shares of its common stock to affiliates of Vivo Capital, LLC and Samsara BioCapital, LP (the "Private Placement Purchasers"), at a purchase price equal to $4.10 per share, which is the price to the public in the public offering. The shares in the private placement were issued pursuant to a stock purchase agreement entered into among the Company and the Private Placement Purchasers.

The net proceeds from the public offering and private placement, after deducting underwriting discounts, placement agent fees and other offering expenses of approximately $10.1 million, were approximately $150.1 million.

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

3. Common Stock (Continued)

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.

4. Net Income (Loss) Per Common Share

Basic and diluted net loss per common share is determined by dividing net loss by the weighted average common shares and pre-funded warrants outstanding during the period. Basic and diluted shares outstanding includes the weighted average effect of the Company's outstanding pre-funded warrants as the exercise of such pre-funded warrants requires nominal consideration to be given for the delivery of the corresponding shares of common stock. As of December 31, 2022, and 2021, the Company had zero and 3,164,280 pre-funded warrants outstanding, respectively, which if exercised, would increase the number of shares of common stock issued and outstanding. 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,		
	2022	2021	2020
Basic and diluted net income (loss) per common share calculation:			
Net loss	$ (185,211)	$ (114,522)	$ (84,547)
Weighted average common shares outstanding - dilutive	121,037	101,866	74,185
Net loss per common share - basic and diluted	$ (1.53)	$ (1.12)	$ (1.14)

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,		
	2022	2021	2020
Stock options outstanding	12,402,629	10,861,483	8,927,698
Restricted stock units	3,025,941	2,246,269	1,958,383
Total	15,428,570	13,107,752	10,886,081

5. Cash, Cash Equivalents and Available-for-Sale Securities

As of December 31, 2022 and December 31, 2021 the Company had cash and cash equivalents of approximately $476.3 million and $261.4 million, respectively. Cash and cash equivalents at December 31, 2022 and December 31, 2021 included cash of $0.6 million and $9.9 million, respectively. As of December 31, 2022 and December 31, 2021, cash and cash equivalents also included $475.7 million and $251.5 million, respectively, of investments in money market funds.

As of December 31, 2022 and December 31, 2021, the Company held available-for-sale securities of approximately $170.5 million and $120.3 million, respectively, all of which have maturities of less than one year.

As of December 31, 2022, the Company determined that there were no credit losses in its available-for-sale securities. Factors considered in determining whether a loss resulted from a credit loss or other factors included the length of time and extent to which the investment’s fair value has been less than the cost basis, the financial condition and near-term prospects of the investee, the extent of the loss related to credit of the issuer, the expected cash flows from the security, the Company’s

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

5. Cash, Cash Equivalents and Available-for-Sale Securities (Continued)

intent to sell the security, and whether or not the Company will be required to sell the security before the recovery of its amortized cost.

The Company classifies these securities as available-for-sale. However, the Company has not sold and does not currently intend to sell its investments and the Company believes it is more likely than not that the Company will recover the carrying value of these investments.

Available-for-sale securities, including carrying value and estimated fair values, are summarized as follows:

	As of December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. Treasury securities	$ 27,481	$ 3	$ (61)	$ 27,423
Corporate debt securities	109,248	—	(119)	109,129
U.S. government agency securities	9,644	25	—	9,669
Asset-backed securities	19,360	—	(63)	19,297
Supranational securities	5,027	—	(14)	5,013
Total	$ 170,760	$ 28	$ (257)	$ 170,531

	As of December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. Treasury securities	$ 18,202	$ —	(16)	$ 18,185
Corporate debt securities	82,138	—	(57)	82,081
Asset-backed securities	16,008	—	(14)	15,995
Supranational securities	4,044	—	(3)	4,041
Total	120,392	—	(90)	120,302

6. Fair Value Measurements

The Company classifies its available-for-sale 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.

In December 2022, IVERIC bio Gene Therapy LL ("Iveric Subsidiary"), the Company's wholly owned subsidiary, entered into an Asset Purchase Agreement (the "Purchase Agreement") with Opus Genetics Inc. ("Opus"), a privately held company, pursuant to which Opus acquired all rights, title and interests in and to Iveric Subsidiary's assets primarily related to the Company's IC-100 and IC-200 product candidates, including the Company's exclusive license agreements with the University of Florida Research Foundation, Incorporated, and the Trustees of the University of Pennsylvania for both product candidates and certain related sponsored research agreements . Under the terms of the Purchase Agreement, the Iveric Subsidiary received (i) an upfront cash payment in the amount of $500,000 and (ii) 2,632,720 shares of Series Seed Preferred Stock of Opus (the "Opus shares"), par value $0.00001 per share, pursuant to a Stock Issuance Agreement (the "Opus SPA") that the parties entered into concurrently with the Purchase Agreement, resulting in the Iveric Subsidiary owning of a high single-digit percentage of the outstanding capital stock of Opus on a fully diluted basis. The Purchase Agreement and the Opus SPA provide for Opus to issue additional shares of capital stock that will maintain Iveric Subsidiary’s ownership at a mid to high single-digit percentage of the fully diluted outstanding capital stock of Opus through Opus’s next round of financing in which it raises a specified minimum amount of gross proceeds. Iveric Subsidiary is also eligible to receive (i) contingent development and regulatory milestone payments of up to $12.8 million and (ii) additional sales milestone payments of up to $98.9 million from Opus. Further, the Iveric Subsidiary will receive, on a country-by-country and product-by-product basis, an earn-out of a low single-digit percentage on net sales of IC-100 and IC-200. The fair value of the contingent consideration was determined to be de minimus.

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

6. Fair Value Measurements (Continued)

In connection with the Purchase Agreement, the Company recognized the Opus shares at a fair value of $1.9 million using an option pricing valuation model that included assumptions for the volatility of Opus common stock (based on the historical volatility of similar companies), weighted time to exit, and market adjustments (Level 3 inputs). The Opus shares are presented within "other assets" in the accompanying Consolidated Balance Sheets.

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, 2022:

	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*	$ 475,689	$ —	$ —
Investments in U.S. Treasury securities	$ 27,423	$ —	$ —
Investments in corporate debt securities	$ —	$ 109,129	$ —
Investments in U.S. government agency securities	—	$ 9,669	—
Investments in asset-backed securities	$ —	$ 19,297	$ —
Investments in supranational securities	$ —	$ 5,013	$ —

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, 2021:

	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*	$ 251,488	$ —	$ —
Investments in U.S. Treasury securities	$ 18,185	$ —	$ —
Investments in corporate debt securities	$ —	$ 82,081	$ —
Investments in asset-backed securities	$ —	$ 15,995	$ —
Investments in supranational securities	—	4,041	—

* Investments in money market funds are reflected in cash and cash equivalents in the accompanying Consolidated 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, 2022 or December 31, 2021.

7. Licensing and Commercialization Agreements

ACP 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

7. Licensing and Commercialization Agreements (Continued)

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, including ACP, 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 $9.0 million in fees based on its achievement of specified clinical milestone events under the C5 License Agreement, including two milestone payments of $1.0 million and $6.0 million, respectively, triggered by the positive 12-month data from, and by completion of, the GATHER1 trial, which the Company paid in March 2020 and October 2020, respectively.

Under the C5 License Agreement, for each anti-C5 aptamer product that the Company may develop under the agreement, including ACP, it is obligated to make additional payments to Archemix of up to an aggregate of $50.5 million if it achieves specified development, clinical and regulatory milestones, with $24.5 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.

License Agreement with University of Massachusetts for the miniCEP290 Program

In July 2019, the Company entered into the miniCEP290 License Agreement with UMass. 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

7. Licensing and Commercialization Agreements (Continued)

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 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.

License Agreement with DelSiTech Ltd.

On June 30, 2022, the Company entered into a license agreement (the "DelSiTech License Agreement") with DelSiTech Ltd. ("DelSiTech"). Under the DelSiTech License Agreement, DelSiTech granted the Company a worldwide, exclusive license under specified patent rights and know-how to develop, have developed, make, have made, use, offer to sell, sell, have sold, otherwise commercialize, export and import ACP using DelSiTech's silica-based sustained release technology for the treatment of diseases of the eye in humans (the "Licensed Product"). The Company may grant sublicenses of the licensed patent rights and know-how without DelSiTech's consent.

The Company paid DelSiTech a €1.25 million upfront license fee, which was recognized as a research and development expense during the three months ended June 30, 2022. Under the DelSiTech License Agreement, the Company is further obligated to pay DelSiTech, up to an aggregate of €35.0 million, if the Company achieves specified clinical and development milestones with respect to the Licensed Product. In addition, the Company is also obligated to pay DelSiTech up to an aggregate of €60.0 million if the Company achieves specified commercial sales milestones with respect to worldwide net sales of the Licensed Product. Due to the uncertainty of the achievement of these milestones, the Company will account for any additional payments if and when such milestones are met.

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

7. Licensing and Commercialization Agreements (Continued)

The Company is also obligated to pay DelSiTech royalties at a low single-digit percentage of net sales of the Licensed Product. The royalties payable by the Company are subject to reduction under specified circumstances. The Company's obligation to pay royalties under the DelSiTech License Agreement will continue on a country-by-country basis until the later of: (a) the expiration of the last-to-expire licensed patent rights covering the Licensed Product in the country of sale, or (b) expiration of all regulatory exclusivity for the Licensed Product in the country of sale. Future milestones and royalties will be recognized in their entirety when achieved.

Unless earlier terminated by the Company or DelSiTech, the DelSiTech License Agreement will expire on a country-by-country basis upon the expiration of the Company's obligation to pay royalties to DelSiTech on net sales of the Licensed Product. Upon expiration of the DelSiTech License Agreement, the licenses granted by DelSiTech to the Company will become fully paid up and irrevocable. The Company may terminate the agreement at any time for any reason upon 60 days' prior written notice to DelSiTech. Either party may also terminate the DelSiTech License Agreement if the other party materially breaches the DelSiTech License Agreement and does not cure such breach within a specified cure period. Following any termination of the DelSiTech License Agreement prior to expiration of the term of the DelSiTech License Agreement, all rights to the licensed patent rights and know-how that DelSiTech granted to the Company will revert to DelSiTech, subject to the Company's right to sell off any Licensed Product in the Company's inventory as of the effectiveness of such termination.

8. Property and Equipment

Property and equipment as of December 31, 2022 and 2021 were as follows:

	Useful Life (Years)	December 31, 2022	December 31, 2021
Research, manufacturing and clinical equipment	5 - 10	$ 548	$ 283
Computer, software and other office equipment	5	1,201	933
Furniture and fixtures	7	203	—
Automobile	5	125	125
		2,077	1,341
Accumulated depreciation		(1,131)	(993)
Property and equipment, net		$ 946	$ 348

For the years ended December 31, 2022, 2021 and 2020, depreciation expense was $138 thousand, $39 thousand and $143 thousand, respectively.

9. 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:

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

9. Income Taxes (Continued)

	Years ended December 31,		
	2022	2021	2020
Percent of pre-tax income:			
U.S. federal statutory income tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	7.3 %	8.1 %	14.8 %
Permanent items	1.8 %	0.7 %	0.2 %
Impact of state rate changes	— %	(3.8)%	0.1 %
Research and development credit	3.7 %	3.3 %	3.1 %
Change in valuation allowance	(33.8)%	(29.3)%	(34.8)%
Effective income tax rate	— %	— %	4.4 %

The components of income tax benefit are as follows:

	Years ended December 31,		
	2022	2021	2020
Current:			
Federal	$ —	$ —	$ —
State	—	—	(3,695)
Deferred:			
Federal	—	—	—
State	—	—	—
Income tax benefit	$ —	$ —	$ (3,695)

Significant components of the Company's deferred tax assets (liabilities) for 2022 and 2021 consist of the following:

	As of December 31,	
	2022	2021
Deferred tax assets (liabilities)		
License and technology payments	$ 4,335	$ 5,356
Share-based compensation	25,677	21,614
Capitalized R&D	27,527	—
Unrecognized losses from securities	65	—
Accrued expenses	483	320
Right-of-use asset	(335)	(430)
Lease obligation	340	444
Depreciation	(23)	1
Federal and state net operating loss carryforwards	190,163	165,401
Research and development credits	20,931	13,742
Other	35	20
Deferred income tax assets	269,198	206,468
Valuation allowance	(269,198)	(206,468)
Net deferred tax assets	$ —	$ —

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

9. Income Taxes (Continued)

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 2022 and 2021. 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 2025. 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. In October 2022, the Company was approved to receive approximately $12.5 million through the State of New Jersey's Technology Business Tax Certificate Transfer Program (the "Program") which allows qualified technology and biotechnology businesses in New Jersey to sell unused amounts of NOLs and defined research and development tax credits. As of December 31, 2022, the Company has not received any funds from the Program. As of December 31, 2022, the Company has federal NOL carryforwards of approximately $658.2 million. Pursuant to Internal Revenue Code (“IRC”) Sections 382 and 383, use of the Company’s federal and state net operating loss and research and development income tax credit carryforwards may be limited in the event of a cumulative change in ownership of more than 50.0% within a three-year period. In October 2021, the Company experienced an ownership change as defined in IRC Section 382. The Company does not anticipate the limitations imposed by IRC Sections 382 and 383 to have a material impact on its ability to utilize net operating losses and credits in future years.

For the years ended December 31, 2022 and 2021, the Company recorded no benefit from income taxes. For the year ended December 31, 2020, the Company recorded an income tax benefit of $3.7 million primarily to reflect the settlements of local tax audits.

On March 27, 2020, in response to the COVID-19 pandemic, the U.S. Congress enacted the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act"). The CARES Act provides numerous tax provisions and other stimulus measures, including the immediate refund of minimum tax credits. In April 2021, the Company received the remaining balance, approximately $1.8 million, of its minimum tax credits refund.

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, 2022.

Pursuant to ASC 740-10, *Accounting for Uncertainty in 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, 2022, there was no change in the Company's uncertain tax liability.

The Company's position with respect to uncertain tax positions is set forth below:

Opening balance	$	6,723
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		—
Gross amount of decreases in unrecognized tax benefits during the period - other		—
Decreases due to settlement with tax authorities during the period		—
Reduction of unrecognized tax benefits due to expiration of the state of limitations during the period		—
Closing Balance	$	6,723

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.

The Company is currently subject to audit by the U.S. Internal Revenue Service, or IRS, for the years 2019 through 2021, and state tax jurisdictions for the years 2018 through 2021. However, the IRS or state tax authorities may still examine

9. Income Taxes (Continued)

and adjust an NOL or R&D credit arising from a closed year to the extent it is utilized in a year that remains subject to audit. The Company's previously filed income tax returns are not presently under audit by the IRS or state tax authorities.

10. Loan and Security Agreement

On July 26, 2022 (the "Closing Date"), the Company and certain of its subsidiaries (the "Subsidiary Borrowers") entered into a Loan and Security Agreement (the "Loan Agreement") with Hercules Capital, Inc. ("Hercules"), in its capacity as administrative agent and collateral agent (in such capacity, the "Agent") and as a lender, Silicon Valley Bank ("SVB") and certain other financial institutions that from time to time become parties to the Loan Agreement as lenders (collectively, the "Lenders"). The Loan Agreement provides for term loans in an aggregate principal amount of up to $250.0 million under multiple tranches (the "2022 Term Loan Facility"), available as follows: (i) a term loan advance in the amount of $50.0 million, which was drawn on the Closing Date; (ii) a second tranche consisting of term loan advances in the aggregate principal amount of $50.0 million which was drawn in December 2022; (iii) a third tranche consisting of term loan advances in the aggregate principal amount of $25.0 million, available at the Company's option through September 30, 2023; (iv) subject to FDA approval of ACP in GA with a label generally consistent with that sought in the Company's NDA ("Milestone 3"), a fourth tranche consisting of term loan advances in the aggregate principal amount of $75.0 million, available at the Company's option beginning on the date that Milestone 3 is achieved and continuing through the earlier of (x) September 30, 2024 and (y) the date that is 90 days after the date that Milestone 3 is achieved; and (v) subject to approval by the Lenders' investment committee in its discretion, a fifth tranche of additional term loans in an aggregate principal amount of up to $50.0 million, available on or before the Amortization Date (as defined below). With the exception of the first $50.0 million tranche drawn on the Closing Date, each of the tranches may be drawn down in $5.0 million increments at the Company's election upon achievement of the relevant conditions specified in the Loan Agreement. The Company has agreed to use the proceeds of the 2022 Term Loan Facility for working capital and general corporate purposes.

Notwithstanding limitations and restrictions imposed by covenants in the Loan Agreement, the Company is permitted to engage in certain specified transactions. For example, the terms of the Loan Agreement provide that the Company may issue convertible notes in an aggregate principal amount of not more than $400.0 million, provided that such notes are unsecured, have a maturity date no earlier than six months following the Maturity Date (as defined below), and meet certain other conditions. The Loan Agreement also provides that the Company may enter into royalty interest financing transactions that are subordinated to the 2022 Term Loan Facility, have a maturity date no earlier than six months following the Maturity Date, and meet certain other conditions. Following the achievement of Milestone 3, the Loan Agreement also provides for a possible additional revolving credit facility of up to $50.0 million, which will be formula-based and backed by the Company's accounts receivables. This potential revolving credit facility is not an existing facility under the Loan Agreement, is not committed, and is subject to agreement among the Company and the Lenders. The Company may enter into non-exclusive and certain specified exclusive licensing arrangements with respect to core intellectual property and non-exclusive and exclusive licensing arrangements or otherwise transfer non-core intellectual property without the consent of the Lenders. The Company may also enter into certain permitted acquisitions, subject to a limit on total cash consideration for acquisitions consummated during specified periods. Additionally, the Company must provide the Lenders the opportunity to invest up to $10.0 million in any equity financing, subject to certain exclusions, that is broadly marketed to multiple investors and in which the Company receives net cash proceeds of $75.0 million or more in any one or series of related financings (or in the case of any such equity financing that is a registered offering, use its commercially reasonable efforts to provide such opportunity to the Lenders).

The 2022 Term Loan Facility will mature on August 1, 2027 (the "Maturity Date"). The outstanding principal balance of the 2022 Term Loan Facility bears interest at a floating interest rate per annum equal to the greater of either (i) (x) the lesser of the Wall Street Journal prime rate and 6.25% plus (y) 4.00% or (ii) 8.75%. The per annum interest rate is capped at 10.25%. Accrued interest is payable monthly following the funding of each term loan. The Company may make payments of interest only, without any loan amortization payments, for a period of 42 months following the Closing Date, which period may be extended to the Maturity Date if (i) Milestone 3 has been achieved and (ii) no default or event of default exists under the Loan Agreement. At the end of the interest only period (the "Amortization Date"), the Company is required to begin repayment of the outstanding principal of the 2022 Term Loan Facility in equal monthly installments.

As collateral for the obligations under the 2022 Term Loan Facility, the Company has granted to the Agent for the benefit of the Lenders a senior security interest in substantially all of its and each Subsidiary Borrower's property, inclusive of intellectual property, with certain limited exceptions set forth in the Loan Agreement.

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

10. Loan and Security Agreement (Continued)

The Loan Agreement contains customary closing and commitment fees, prepayment fees and provisions, events of default and representations, warranties and affirmative and negative covenants, including a financial covenant requiring the Company to maintain certain levels of cash in accounts subject to a control agreement in favor of the Agent (the "Qualified Cash") during the period commencing on May 15, 2023 through August 14, 2024. Commencing on August 15, 2024, the Company will also be required to maintain a certain minimum amount of trailing six-month net product revenue from the sale of ACP, tested on a quarterly basis. The revenue covenant will be waived at any time at which the Company (x) (i) maintains a market capitalization in excess of $600.0 million and (ii) maintains Qualified Cash in an amount greater than or equal to fifty percent (50%) of the outstanding 2022 Term Loan Facility at such time or (y) maintains Qualified Cash in an amount greater than or equal to ninety percent (90%) of the outstanding 2022 Term Loan Facility at such time. Upon the occurrence of an event of default, including a material adverse effect, subject to certain exceptions, on the business, operations, properties, assets or financial condition of the Company and the Subsidiary Borrowers taken as a whole, and subject to any specified cure periods, all amounts owed by the Company may be declared immediately due and payable by the Lenders. As of December 31, 2022, the Company was in compliance with all applicable covenants under the Loan Agreement.

In addition, the Company is required to make a final payment fee (the "End of Term Charge") upon the earlier of (i) the Maturity Date or (ii) the date the Company prepays, in full or in part, the outstanding principal balance of the 2022 Term Loan Facility. The End of Term Charge is 4.25% of the aggregate original principal amount of the term loans repaid or prepaid under the Loan Agreement.

The Company may, at its option, prepay the term loans in full or in part, subject to a prepayment penalty equal to (i) 2.0% of the principal amount prepaid if the prepayment occurs prior to the first anniversary of the Closing Date, (ii) 1.5% of the principal amount prepaid if the prepayment occurs on or after the first anniversary and prior to the second anniversary of the Closing Date, and (iii) 0.75% of the principal amount prepaid if the prepayment occurs on or after the second anniversary and prior to the third anniversary of the Closing Date.

During the year ended December 31, 2022, the Company recognized interest expense on its Consolidated Statements of Operations and Comprehensive Loss in connection with the 2022 Term Loan Facility as follows:

	Year ended December 31, 2022
Interest expense for 2022 Term Loan Facility	$ 2,486
Accretion of end of term charge	215
Amortization of debt issuance costs	251
Total interest expense related to 2022 Term Loan Facility	$ 2,952

The principal balance of the 2022 Term Loan Facility and related accretion and amortization as of December 31, 2022, were as follows:

	December 31, 2022
2022 Term Loan Facility, gross (amount drawn)	$ 100,000
Debt issuance costs	(3,898)
Accretion of end of term charge	215
Accumulated amortization of debt issuance costs	251
2022 Term Loan Facility, net	$ 96,568

11. Operating Leases

The Company leases office spaces located in Parsippany, New Jersey and Cranbury, New Jersey under non-cancelable operating lease arrangements. The Company's Parsippany, New Jersey office space lease expires in August 2023 and the Company's Cranbury, New Jersey office space lease expires in February 2024.

For the years ended December 31, 2022, 2021 and 2020, lease and rent expense was $1.4 million, $0.7 million, and $0.6 million, respectively. Cash paid from operating cash flows for amounts included in the measurement of lease liabilities

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

11. Operating Leases (Continued)

was $1.4 million and $0.7 million for the years ended December 31, 2022 and 2021, respectively. At December 31, 2022, the Company's operating leases had a weighted average remaining lease term of 0.7 years and a weighted average estimated incremental borrowing rate of 5.6%.

The following presents the maturity of the Company's operating lease liabilities as of December 31, 2022:

	December 31, 2022
2023	1,216
2024	11
Total minimum lease payments	1,227
Less imputed interest	(27)
Present value of minimum lease payments	1,200
Less current portion	1,189
Total long-term operating lease liabilities	$ 11

12. Commitments and Contingencies

ACP - Archemix Corp.

The Company is party to an agreement with Archemix Corp. (“Archemix”) under which the Company in-licensed rights in certain patents, patent applications and other intellectual property related to ACP and pursuant to which the Company may be required to pay sublicense fees and make milestone payments (the “C5 License Agreement”). Under the C5 License Agreement, for each anti-C5 aptamer product that the Company may develop under the agreement, including ACP, the Company is obligated to make additional payments to Archemix of up to an aggregate of $50.5 million if the Company achieves specified development, clinical and regulatory milestones, with $24.5 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 products licensed under the agreement. The Company is also obligated to pay Archemix a double-digit percentage of specified non-royalty payments the Company may receive from any sublicensee of its rights under the C5 License Agreement. The Company is not obligated to pay Archemix a running royalty based on net product sales in connection with the C5 License Agreement.

ACP Sustained Release Delivery Technology - DelSiTech

Under the DelSiTech License Agreement with DelSiTech, the Company is obligated to make payments up to an aggregate of €35.0 million, if the Company achieves specified clinical and development milestones with respect to a Licensed Product. In addition, the Company is also obligated to pay DelSiTech up to an aggregate of €60.0 million if the Company achieves specified commercial sales milestones with respect to worldwide net sales of the Licensed Product. The Company is also obligated to pay DelSiTech royalties at a low single-digit percentage of net sales of the Licensed Product. The royalties payable by the Company are subject to reduction under specified circumstances.

miniCEP290 Program - University of Massachusetts

Under its exclusive license agreement with the University of Massachusetts (“UMass”) for its miniCEP290 program, which targets LCA10, which is associated with mutations in the *CEP290* gene, 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

12. Commitments and Contingencies (Continued)

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.

IC-500 - Former Equityholders of Inception 4

Under the agreement and plan of merger between the Company and Inception 4, Inc. ("Inception 4"), pursuant to which the Company acquired IC-500 and its other HtrA1 inhibitors (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 IC-500 or any other 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 acquisition, 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 acquisition, 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 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. Ophthotech Corporation, et al., No. 1:17-cv-00210. On March 9, 2017, a related putative class action lawsuit was filed against the Company and the same group of its current and former executive officers in the United States District Court for the Southern District of New York, captioned Wasson v. Ophthotech Corporation, et al., No. 1:17-cv-01758. These cases were consolidated on March 13, 2018. On June 4, 2018, the lead plaintiff filed a consolidated amended complaint (the "CAC"). The CAC purports to be brought on behalf of shareholders who purchased the Company's common stock between March 2, 2015 and December 12, 2016. The CAC generally alleges that the Company and certain of its officers violated Sections 10(b) and/or 20(a) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder by making allegedly false and/or misleading statements concerning the results of the Company's Phase 2b trial and the prospects of the Company's Phase 3 trials for Fovista in combination with anti-VEGF agents for the treatment of wet AMD. The CAC seeks unspecified damages,

12. Commitments and Contingencies (Continued)

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. On June 12, 2020, the lead plaintiff filed a motion for class certification. On August 11, 2020, the defendants filed a notice of non-opposition to lead plaintiff's motion for class certification. On April 23, 2021, the court issued an order staying the action until July 1, 2021, 10 days after a mediation scheduled for June 21, 2021. On July 1, 2021, following the June 21, 2021 mediation, the parties notified the court that they had reached an agreement in principle to settle the class action. On September 8, 2021, the parties executed a settlement agreement and submitted the agreement to the court for approval. Under the terms of the settlement agreement, the Company agreed to pay $29 million, which includes the attorneys' fees and costs and expenses for the plaintiffs' counsel. On March 17, 2022, the court provided a preliminary approval of the settlement. In April 2022, the Company's insurance carriers paid the full amount of the settlement directly to the plaintiffs' escrow account. On September 16, 2022, the court granted final approval of the settlement. This settlement did not have a material impact on the Company's financial condition.

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 ("SLC") of the Company's board of directors. On February 18, 2020, the Company filed an answer to the complaint. The Company and the plaintiff agreed to stay this litigation while the SLC conducts its investigation. On May 4, 2020, the court approved the stipulation and stayed the litigation through November 1, 2020. By agreement of the parties, the court has since extended the stay through June 26, 2021. The Company also entered into tolling agreements with the defendant directors to December 2022. On January 27, 2022, the parties executed a settlement agreement (the "Stipulation of Settlement"). On November 3, 2022, the court issued an order preliminarily approving the settlement. On January 27, 2023, the court granted final approval of the settlement. This settlement did not have a material impact on the Company's financial condition.

On October 16, 2018, the Company's board of directors received a shareholder demand to investigate and commence legal proceedings against certain members of the Company's board of directors. The demand alleges facts that are substantially similar to the facts alleged in the CAC and the Pacheco complaint and asserts claims that are substantially similar to the claims asserted in the Pacheco complaint. On January 30, 2019, the Company's board of directors received a second shareholder demand from a different shareholder to investigate and commence legal proceedings against certain current and former members of the Company's board of directors based on allegations that are substantially similar to the allegations contained in the first demand letter. These shareholder demands were referred to a demand review committee of the Company's board of directors. On May 6, 2021, the shareholders who served the October 16, 2018 demand filed a shareholder derivative action against current and former members of the Company's board of directors and certain current and former officers of the Company in the New York Supreme Court, captioned Brian Ferber et al., derivatively on behalf of Ophthotech Corporation v. Axel Bolte et al., Index No. 154462/2021. The complaint asserts the same claims as those asserted in the Pacheco complaint and is based on factual allegations that are materially similar to the allegations in the Pacheco complaint. On June 22, 2021, the parties filed a stipulation staying the Ferber action until 60 days after the SLC concludes its investigation. On January 27, 2022, the parties executed the Stipulation of Settlement referred to above, settling the matter. On November 3, 2022, the court issued an order preliminarily approving the settlement. On January 27, 2023, the court granted final approval of the settlement. The settlement did not have a material impact on the Company's financial condition.

13. 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 18,166,000 additional shares to the 2013 Plan, including for 2023, an increase of approximately 2,542,000 shares. As of December 31, 2022, the Company had approximately 166,000 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. In March 2020, the Company's board of directors amended the 2019 Inducement Plan to reserve an additional 1,000,000 shares of its common stock for issuance under the plan and in February 2021, the Company's board of directors further amended the 2019 Inducement Plan to reserve an additional 600,000 shares of its common stock for issuance under the plan. In September 2021, December 2021 and May 2022, the Company's board of directors further amended the 2019 Inducement Plan to reserve an additional 1,000,000 shares of common stock for issuance under the plan during each of the instances. In February 2023, the Company's board of directors further amended the 2019 Inducement Plan to reserve an additional 2,000,000 shares of common stock for issuance under the plan. The terms and conditions of the 2019 Inducement Plan are substantially similar to those of the 2013 Plan. As of December 31, 2022, the Company had approximately 791,000 shares available for grant under the 2019 Inducement Plan.

In April 2016, the board of directors adopted the ESPP pursuant to which the Company may sell up to an aggregate of 1,000,000 shares of common stock. The ESPP was approved by the Company's stockholders in June 2016. The ESPP allows eligible employees to purchase common stock at a price per share equal to 85% of the lower of the fair market value of the common stock at the beginning or end of each six month offering period during the term of the ESPP. The first offering period began in September 2016. In December 2022, the ESPP was amended to permit employees to enroll any of four times each year.

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

A summary of the stock option activity, weighted average exercise prices, options outstanding and exercisable as of December 31, 2022, 2021 and 2020 is as follows (in thousands except weighted average exercise price):

	Years ended December 31,					
	2022		2021		2020	
	Common Stock Options	Weighted Average Exercise Price	Common Stock Options	Weighted Average Exercise Price	Common Stock Options	Weighted Average Exercise Price
Outstanding, December 31, 2021	10,861	$ 10.94	8,928	$ 9.22	6,780	$ 10.89
Granted	3,812	$ 19.48	3,204	$ 13.03	2,630	$ 6.10
Exercised	(2,066)	$ 3.84	(646)	$ 2.80	(109)	$ 2.89
Expired or forfeited	(204)	$ 14.08	(625)	$ 8.87	(373)	$ 19.49
Outstanding, December 31, 2022	12,403	$ 14.70	10,861	$ 10.94	8,928	$ 9.22

	Years ended December 31,		
	2022	2021	2020
Options exercisable at December 31, 2022	5,457	5,584	4,462
Weighted average grant date fair value (per share) of options granted during the period	$ 13.57	$ 10.53	$ 4.83

As of December 31, 2022, there were approximately 11,847,000 options outstanding, net of estimated forfeitures, that had vested or are expected to vest. The weighted-average exercise price of these options was $14.66 per option; the weighted-average remaining contractual life of these options was 7.5 years; and the aggregate intrinsic value of these options was approximately $106.2 million. A summary of the stock options outstanding and exercisable as of December 31, 2022 is as follows (in thousands except exercise prices and weighted average exercise price):

	December 31, 2022				
	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
$1.20-$2.96	1,266	5.3	$ 2.43	1,263	$ 2.43
$2.97-$4.88	1,280	6.1	$ 4.02	1,021	$ 4.08
$4.89-$8.07	2,319	7.8	$ 6.73	1,171	$ 6.58
$8.08-$15.00	2,644	8.6	$ 12.88	705	$ 12.67
$15.01-$73.22	4,894	7.9	$ 25.43	1,297	$ 38.68
	12,403	7.6	$ 14.70	5,457	$ 13.57
Aggregate Intrinsic Value	$ 109,659			$ 66,270	

Cash proceeds from, and the aggregate intrinsic value of, stock options exercised during the years ended December 31, 2022, 2021 and 2020, respectively, were as follows:

	Years ended December 31,		
	2022	2021	2020
Cash proceeds from options exercised	$ 7,943	$ 1,808	$ 314
Aggregate intrinsic value of options exercised	$ 23,628	$ 4,997	$ 393

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

In connection with stock option awards granted to employees, non-employees directors and certain other individuals, the Company recognized approximately $16.1 million, $6.5 million and $4.7 million in share-based compensation expense during the years ended December 31, 2022, 2021 and 2020, respectively, net of expected forfeitures. As of December 31, 2022, there were approximately $66.9 million of unrecognized compensation costs, net of estimated forfeitures, related to stock option awards grants, which are expected to be recognized over a remaining weighted average period of 3.2 years.

The following table presents a summary of the Company's outstanding RSU awards granted as of December 31, 2022 (in thousands except weighted average grant-date fair value)

	Restricted Stock Units	Weighted Average Grant-Date Fair Value
Outstanding, December 31, 2021	2,246	$ 9.82
Awarded	1,565	$ 19.15
Vested	(739)	$ 7.81
Expired or forfeited	(46)	$ 10.96
Outstanding, December 31, 2022	3,026	$ 15.12

As of December 31, 2022, there were approximately 2,788,000 RSUs outstanding, net of estimated forfeitures, that are expected to vest. The weighted-average fair value of these RSUs was $15.12 per share; and the aggregate intrinsic value of these RSUs was approximately $59.7 million.

In connection with RSUs granted to employees, non-employees directors and certain other individuals, the Company recognized approximately $10.2 million, $4.6 million and $3.3 million in share-based compensation expense during the years ended December 31, 2022, 2021, and 2020, respectively, net of expected forfeitures. As of December 31, 2022, there was approximately $36.4 million of unrecognized compensation costs, net of estimated forfeitures, related to RSU grants, which are expected to be recognized over a remaining weighted average period of 3.3 years. The total fair value of the RSUs that vested during the year ended December 31, 2022, was $5.8 million.

In connection with the ESPP made available to employees, the Company recognized approximately $0.4 million and $0.2 million of share-based compensation expense during the years ended December 31, 2022, and December 31, 2021, respectively, net of expected forfeitures. As of December 31, 2022, there was $0.1 million of unrecognized compensation costs, net of estimated forfeitures, related to the ESPP, which are expected to be recognized over 0.2 years. There were 41,016 and 51,951 shares of common stock issued under the ESPP during the year ended December 31, 2022, and 2021, respectively. Cash proceeds from ESPP purchases were approximately $0.5 million and $0.3 million during the year ended December 31, 2022, and 2021, respectively. As of December 31, 2022, 712,394 shares were available for future purchases under the ESPP.

14. 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 $1.0 million, $0.6 million and $0.3 million during the years ended December 31, 2022, 2021, and 2020, respectively.