Ocular Therapeutix™

2022 ANNUAL REPORT

TRANSFORMING OPHTHALMIC CARE
WITH INNOVATIVE THERAPIES

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Ocular Therapeutix is a biopharmaceutical company developing transformational treatments that enhance people's vision and quality of life.

PIPELINE

PROGRAM	THERAPEUTIC FOCUS	PRECLINICAL | CLINICAL | FDA APPROVAL	MILESTONES
Dextenza® (dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use	Post surgical ocular inflammation and pain Ocular itching associated with allergic conjunctivitis		
OTX-TKI (axitinib intravitreal implant)	Wet AMD*		**Q3 2023** Initiate pivotal trial†
OTX-TKI (axitinib intravitreal implant)	Diabetic Retinopathy		**Q1 2024** Initiate pivotal trial†‡
OTX-TIC (travoprost intracameral implant)	Glaucoma and ocular hypertension		**Q4 2023** Topline data from Phase 2 trial
OTX-DED (dexamethasone intracanalicular insert)	Episodic dry eye disease		**Q2 2023** Initiation of trial to determine appropriate placebo comparator for pivotal trial
OTX-CSI (cyclosporine intracanalicular insert)	Dry eye disease		**Q2 2023** Initiation of trial to determine appropriate placebo comparator for pivotal trial
Complement Inhibitor (product candidate)	Dry AMD*		
Gene Delivery (intravitreal and suprachoroidal delivery)	Inherited and acquired ocular diseases		

*Age-related Macular Degeneration (AMD)
†Subject to FDA discussions of future clinical trial requirements and obtaining necessary financing; ‡confirmatory Phase 1 readout

Dear Shareholders,

2022 was a year of tremendous progress at Ocular Therapeutix. On the commercial side of the business, DEXTENZA® recorded net product sales of $50.5M, growing 20% over the prior year. Most importantly, the year ended with fourth quarter net product revenue from DEXTENZA of $13.9M, growing 17% over the prior quarter and 14% over the comparable quarter of 2021. The way the year ended is especially significant as it signaled a return to growth and set a platform for a 2023 with great expectations.

In pipeline development, 2022 proved to be a pivotal year in the history of Ocular Therapeutix. Most notably, we presented interim 7-month data from our U.S. Phase 1 clinical trial comparing OTX-TKI, our axitinib-containing hydrogel intravitreal implant for the treatment of wet age-related macular degeneration, or wet AMD, and other Vascular Endothelial Growth Factor (VEGF)-mediated retinal diseases, against an arm dosed every 8 weeks with aflibercept (EYLEA) at the American Academy of Ophthalmology Annual Meeting in September. The data showed greater than 90% reduction in treatment burden and demonstrated a 73% rescue-free rate up to 7 months after the OTX-TKI injection. Most importantly, the cohort treated with OTX-TKI maintained Best Corrected Visual Acuity (BCVA) and Central Subfield Foveal Thickness (CSFT) measures comparable to the aflibercept comparator arm. In February 2023, we released the 10-month interim analysis that showed no additional rescues in the group of patients who were rescue-free up-to month 7, and continued comparability of BCVA and CSFT measures relative to the aflibercept arm. The results continue to

"In pipeline development, 2022 proved to be a pivotal year in the history of Ocular Therapeutix."

Antony Mattessich
President and Chief Executive Officer

> **"The future is exciting for Ocular Therapeutix and, more importantly, for patients suffering from some of the most common diseases of the eye."**

support our belief that OTX-TKI has the potential to set a new standard of care for durability in the treatment of wet AMD and other VEGF-related retinal diseases.

The rest of the clinical stage pipeline continued to progress in 2022. In 2022, we began enrollment of subjects in our Phase 2 clinical trial of OTX-TIC, our travoprost-containing hydrogel intracameral implant for the treatment of patients with primary open-angle glaucoma or ocular hypertension. In this trial, we are evaluating whether treatment with OTX-TIC can reduce intraocular pressure (IOP) at 8:00AM, 10:00AM, and 4:00PM at the timepoints of 2, 6, and 12 weeks without any adverse effect on endothelial cell-health. If we can demonstrate that OTX-TIC both lowers IOP and maintains its safety profile in chronic dosing, we believe we can create a new market between eye-drop therapies and surgical interventions for patients suffering from glaucoma.

In our dry-eye programs, OTX-CSI, our cyclosporin-containing intracanalicular insert for chronic treatment of dry eye and OTX-DED, our dexamethasone-containing intracanalicular insert for the short-term treatment of episodic dry eye, Phase 2 clinical trial read-outs demonstrated potential benefits in patients with active disease relative to baseline. In both programs, we believe the key to moving forward will be to select an appropriate placebo comparator for future trials through a small study set to begin in the first half of 2023.

In summary, we believe 2022 has put the business on sound footing for the future. DEXTENZA has returned to a pathway of growth and all clinical-stage programs continue to move toward Phase 3 pivotal trial readiness as their next steps in development. The future is exciting for Ocular Therapeutix and, more importantly, for patients suffering from some of the most common diseases of the eye. I would like to thank all the people of Ocular Therapeutix who have worked diligently to get us into this position as well as the providers and patients in our clinical trials. Finally, I would like to thank our shareholders for continuing to believe in the promise of our products and product candidates.

Antony Mattessich
President and Chief Executive Officer

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 001-36554

Ocular Therapeutix, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**20-5560161**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
24 Crosby Drive Bedford, MA	**01730**
(Address of principal executive offices)	**(Zip Code)**

(781) 357-4000

(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**OCUL**	**Nasdaq Global 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. ☒

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

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

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

As of June 30, 2022, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $284 million. The number of shares outstanding of the registrant's class of common stock, as of March 1, 2023: 77,509,134.

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 Stockholders, 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," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "goals," "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:

- our ongoing and planned clinical trials, including our Phase 1 clinical trials of OTX-TKI for the treatment of wet age-related macular degeneration, or wet AMD, our Phase 1 clinical trial of OTX-TKI for the treatment of diabetic retinopathy, our Phase 2 clinical trial of OTX-TIC for the reduction of intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension, our clinical trial to evaluate DEXTENZA® in pediatric subjects following cataract surgery and our planned pivotal clinical trials of OTX-TKI for the treatment of wet AMD and the treatment of diabetic retinopathy;

- our commercialization efforts for our product DEXTENZA;

- our plans to develop, seek regulatory approval for and commercialize OTX-TKI, OTX-TIC, OTX-DED, OTX-CSI, and our other product candidates based on our proprietary bioresorbable hydrogel technology platform;

- our ability to manufacture DEXTENZA and our product candidates in compliance with Current Good Manufacturing Practices and in sufficient quantities for our clinical trials and commercial use;

- the timing of and our ability to submit applications and obtain and maintain regulatory approvals for DEXTENZA, and our product candidates;

- our estimates regarding future revenue; expenses; the sufficiency of our cash resources; our ability to fund our operating expenses, debt service obligations and capital expenditure requirements; and our needs for 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 potential advantages of DEXTENZA and our product candidates;

- the rate and degree of market acceptance and clinical utility of our products;

- our ability to secure and maintain reimbursement for our products as well as the associated procedures to insert, implant or inject our products;

- our estimates regarding the market opportunity for DEXTENZA and our product candidates;

- our license agreement and collaboration with AffaMed Therapeutics Limited under which we are collaborating on the development and commercialization of DEXTENZA and our product candidate OTX-TIC in mainland China, Taiwan, Hong Kong, Macau, South Korea, and the countries of the Association of Southeast Asian Nations;

- our capabilities and strategy, and the costs and timing of manufacturing, sales, marketing, distribution and other commercialization efforts with respect to DEXTENZA, ReSure Sealant and any additional products for which we may obtain marketing approval in the future;

- our intellectual property position;
- our ability to identify additional products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- the impact of government laws and regulations; and
- our competitive position.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures, licensing agreements 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 included in this Annual Report on Form 10-K are made as of the date of this Annual Report on Form 10-K. We do not assume, and we expressly disclaim, any obligation or undertaking 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. All of the market data used in this Annual Report on Form 10-K involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. While we believe that the information from these industry publications, surveys and studies is reliable, we have not independently verified such data. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of important factors, including those described in the section titled "Risk Factors."

This Annual Report on Form 10-K contains references to our trademarks and service marks and to those belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus and the documents incorporated by reference herein may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

SUMMARY OF RISKS RELATED TO OUR BUSINESS

Our business, financial condition, results of operations, future growth prospects and common stock price are subject to numerous risks and uncertainties that you should be aware of before making an investment decision, as more fully described under the heading "Risk Factors" and elsewhere in this Annual Report on Form 10-K. These risks include, but are not limited to, the following:

- We have a history of incurring significant losses. Our net loss was $71.0 million for the year ended December 31, 2022, primarily due to a loss from operations of $78.7 million offset by a change in fair value of a derivative liability of $13.8 million. Our net loss was $6.6 million for the year ended December 31, 2021, primarily due to a loss from operations of $78.0 million and a change in fair value of a derivative liability of $78.1 million. As of December 31, 2022, we had an accumulated deficit of $616.8 million. We expect to incur operating losses over the next several years and may never achieve or maintain profitability.
- We will need substantial additional funding. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or our commercialization efforts. To the extent that we raise additional capital through the sale of equity, preferred

equity or convertible debt securities, our stockholders' ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our existing stockholders' rights as holders of our common stock. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

- If we raise additional funds through collaborations, strategic alliances, licensing arrangements, royalty agreements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs, 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 or other arrangements when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

- We depend heavily on the success of DEXTENZA and our product candidates. Our ability to generate product revenues sufficient to achieve profitability is dependent on our successful commercialization of DEXTENZA for the treatment of ocular inflammation and pain following ophthalmic surgery and ocular itching associated with allergic conjunctivitis and our obtaining marketing approval for and successfully commercializing our product candidates.

- Clinical trials of our product candidates may not be successful. If we experience delays or difficulties in enrollment, serious adverse events or side effects are identified, or any other unforeseen events occur in connection with clinical trials of any of our product candidates, or if clinical trials of any of our product candidates fail to demonstrate safety and efficacy to the satisfaction of the FDA or other regulatory authorities or do not otherwise produce favorable results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of such product candidates.

- We may not be successful in our efforts to develop additional products and product candidates based on our bioresorbable hydrogel technology platform or to expand the use of our bioresorbable hydrogel technology for treating additional ophthalmic diseases and conditions.

- We have a single-site clinical and commercial manufacturing facility. We also depend from time to time on single-source suppliers for certain materials used in the manufacturing of our products and product candidates. If we have a material disruption in our manufacturing operations at this facility, or if we are unable to obtain sufficient components of our products and product candidates from our suppliers on acceptable terms or at all, we may not have sufficient quantities of our product candidates to meet our clinical trial requirements or of our product inventory to meet our commercial requirements. Such an event could delay our clinical trials or, particularly because we maintain limited commercial inventory, could reduce our product sales.

- DEXTENZA and any product candidates for which we obtain marketing approval may become subject to unfavorable pricing regulations, third-party coverage or reimbursement practices or healthcare reform initiatives, which could harm our business. If DEXTENZA ceases to be eligible for reimbursement separate from ophthalmic surgery, our net product revenues would decline significantly, and our ability to generate revenues from future sales of DEXTENZA would be adversely affected. CMS has also adopted fixed reimbursement amounts for the procedure of inserting DEXTENZA that are lower than the prior procedure reimbursement levels, and there can be no assurance the rates will not be further reduced in the future. A low procedure reimbursement could adversely impact our ability to generate revenues related to DEXTENZA.

- If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, maintain regulatory compliance for our manufacturing operations, obtain and maintain patent protection for or gain market acceptance by physicians, patients and third-party payors and others in the medical community of DEXTENZA or any of our product candidates for which we obtain marketing approval, or experience significant delays in doing so, our business will be materially harmed and our ability to generate revenues from product sales will be materially impaired.

- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy.

- Our products face and, if approved, our product candidates will face competition from generic and branded versions of existing drugs, many of which have achieved widespread acceptance among physicians, payors and patients for the treatment of ophthalmic diseases and conditions. In addition, because the active pharmaceutical ingredients in our products and leading product candidates are available on a generic basis, competitors will be able to offer and sell products with the same active pharmaceutical ingredient as our products so long as these competitors do not infringe our patent rights.

- Even if we successfully obtain marketing approval for one or more of our product candidates, the approved product will be subject to ongoing review and extensive regulation.

- Our stock price may be volatile and fluctuate substantially. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price at which they purchased it. We have previously, and we may in the future, be the target of legal proceedings related to declines in our stock price.

PART I

Item 1. Business

We are a biopharmaceutical company focused on the formulation, development, and commercialization of innovative therapies for diseases and conditions of the eye using our proprietary bioresorbable hydrogel-based formulation technology. Our mission is to build an ophthalmology-focused biopharmaceutical company that capitalizes on the gaps that we believe increasingly exist in the ophthalmology sector between single product companies and large, multi-product pharmaceutical companies.

Our current products and product candidates in clinical development incorporate therapeutic agents that have previously received regulatory approval from the U.S. Food and Drug Administration, or FDA, including small molecules, into our proprietary bioresorbable hydrogel-based formulation technology in our internal drug development activities, with the goal of providing local programmed release to tailor the duration and amount of drug to be delivered to the eye. We believe that our local programmed-release drug delivery technology has the potential to enable the treatment of conditions and diseases of both the front and the back of the eye and can be administered through a range of different modalities including intravitreal implants, intracameral implants and intracanalicular inserts.

We are currently commercializing DEXTENZA, an intracanalicular insert for the treatment of both post-surgical ocular inflammation and pain and ocular itching associated with allergic conjunctivitis, in the United States. We also have product candidates in preclinical and clinical development:

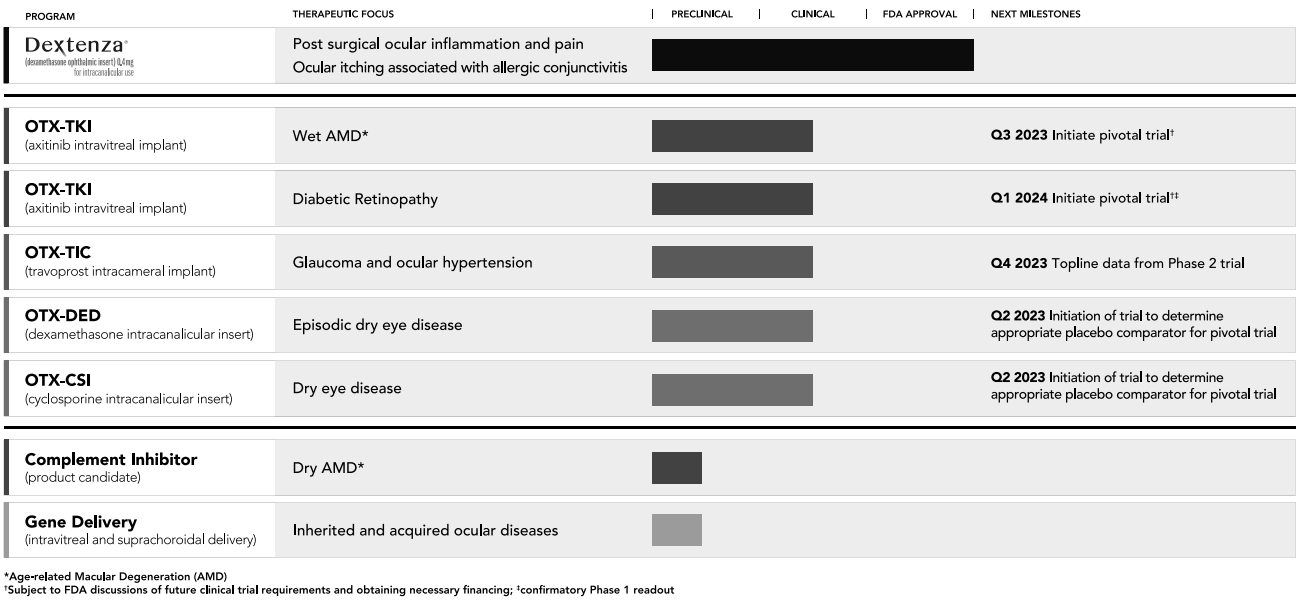
- OTX-TKI, an axitinib intravitreal implant being developed for the treatment of wet age-related macular degeneration, or wet AMD, diabetic retinopathy and other retinal diseases;
- OTX-TIC, a travoprost intracameral implant being developed for the reduction of intraocular pressure, or IOP, in patients with primary open-angle glaucoma or ocular hypertension;
- OTX-DED, a dexamethasone intracanalicular insert being developed for the short-term treatment of the signs and symptoms of dry eye disease;
- OTX-CSI, a cyclosporine intracanalicular insert being developed for the chronic treatment of dry eye disease;
- A complement inhibitor program in preclinical development for the treatment of dry age-related macular degeneration, or dry AMD; and
- A gene delivery program in preclinical development using our hydrogel technology to control the release of vectors such as adeno-associated virus , or AAV, to ocular tissues for the treatment of inherited and acquired ocular diseases, including dry or wet AMD.

We currently focus on some of the largest markets in ophthalmology. According to the Market Scope 2022-2023 reports, our product candidates seek to address select indications within segments of ophthalmology that, in the aggregate, account for approximately $25 billion in global annual sales.

The following table summarizes the status of DEXTENZA, our primary marketed product, and our key product candidates and development programs. We hold worldwide exclusive commercial rights to the core technology underlying all of our product candidates in development and have not granted commercial rights to any marketing

partners other than a license agreement and collaboration with AffaMed for the development and commercialization of DEXTENZA and OTX-TIC in the geographies agreed to between the parties.

PIPELINE AT A GLANCE



*Age-related Macular Degeneration (AMD)
†Subject to FDA discussions of future clinical trial requirements and obtaining necessary financing; ‡confirmatory Phase 1 readout

Our Strategy

Our mission is to build an ophthalmology-focused biopharmaceutical company that capitalizes on the gaps that we believe increasingly exist in the ophthalmology sector between single product companies and large, multi-product pharmaceutical companies. Our strategy is to continue to build upon our experience in commercializing ophthalmology products that can be administered primarily in the surgical and/or office settings and to continue to develop a clinical pipeline of innovative ophthalmology products that address large areas of unmet need. The key tactics of our strategy are:

- *Grow DEXTENZA revenues primarily through sales for the treatment of ocular inflammation and pain following ophthalmic surgery.*

- *Advance our clinical development programs.*
    - OTX-TKI:
        - Wet AMD: be prepared to initiate a pivotal clinical trial as early as the third quarter of 2023, subject to ongoing discussions with the FDA and obtaining the necessary financing to fund the trial, which could be provided through a strategic alliance.
        - Diabetic Retinopathy: be positioned to initiate a pivotal clinical trial as early as the first quarter of 2024 subject to favorable interim results from our ongoing Phase 1 clinical trial, discussions with the FDA and obtaining the necessary financing to fund the trial.
    - OTX-TIC: continue to enroll our U.S.-based Phase 2 clinical trial for the treatment of open-angle glaucoma or ocular hypertension and plan to provide topline data from the trial in the fourth quarter of 2023.
    - Dry Eye Disease – OTX-DED and OTX-CSI: initiate a small trial of OTX-DED in the first half of 2023 to identify a proper placebo control for any future trials of these product candidates.

- *Leverage our commercial infrastructure for additional ophthalmology products for both the surgical and office settings.*

- *Continue to develop experience and expertise with buy-and-bill products.* DEXTENZA and all of our product candidates are designed to be medical-benefit "buy-and-bill" products with associated procedure codes. Products with these characteristics are designed to be attractive not only to physicians, optometrists and patients but also to the sites of care that participate in utilization.

- *Apply our local programmed-release hydrogel-based formulation technology to create additional proprietary solutions for additional ophthalmic diseases and conditions.*

- *Address rest-of-world commercial opportunities through licensing and collaboration agreements.*

Limitations of Current Drug Delivery in Ophthalmology

Eye Drops

Eye drops are widely used to deliver medications directly to the ocular surface and to intraocular tissue in the front of the eye. Eye drops are administrable by the patient or care provider, inexpensive to produce and treat the local tissue. However, eye drops have significant limitations, especially when used for chronic diseases or when requiring frequent administration, including:

- *Lack of patient compliance*. Eye drops require frequent administration, and, as a result, patient compliance with required dosing regimens frequently suffers. Poor patient compliance can lead to diminished efficacy and disease progression.

- *Difficulty in administration*. Eye drops are difficult to administer for many patients, particularly among the elderly, due to physical or mental conditions such as arthritis or dementia. We believe that this also may play a large role in lack of patient compliance and resulting diminished efficacy of treatment.

- *Need for high concentrations*. After eye drops are administered to the ocular surface, the tear film rapidly renews. Most topically applied solutions are washed away by new tear fluid within 15 to 30 seconds. Because contact time with the ocular surface is short, less than 5% of the applied dose actually penetrates to reach intraocular tissues. As a result, eye drops generally require frequent administration at high drug concentrations to deliver a meaningful amount of drug to the eye. This pulsed therapy results in significant variations in drug concentrations over a treatment period, which we refer to as peak and valley dosing. At peak levels, the high concentrations can result in side effects, such as burning, stinging, redness of the clear membrane covering the white part of the eye, referred to as hyperemia, and spikes in IOP, which may lead to drug induced glaucoma. At low concentration levels, the drug may not be effective, thus allowing the disease to progress.

- *Side effects of preservatives*. To guard against contamination, many eye drops are formulated with antimicrobial preservatives, most commonly benzalkonium chloride, or BAK. Patients on long term or chronic therapy, such as glaucoma patients, often suffer reactions, which have been linked to BAK, including burning, stinging, hyperemia, irritation and eye dryness. Less frequently, conjunctivitis or corneal damage may result.

As a result of these limitations, eye drops are often suboptimal as a therapeutic option for the treatment of many diseases and conditions of the front of the eye**.**

Back-of-the-Eye Injections

An intravitreal injection is a procedure to place a medication directly into the space in the back of the eye called the vitreous cavity, which is filled with a jelly-like fluid called the vitreous humor gel. The procedure is usually performed by a trained retina specialist in the office setting. Intravitreal injections are used to administer medications to treat a variety of chronic conditions; wet AMD, diabetic retinopathy, diabetic retinal edema, or DME, and retinal vein

occlusion, or RVO, are among the most common conditions treated with intravitreal anti-VEGF drugs. Anti-VEGF drugs and steroids help to reduce fluid leakage associated with these disorders.

While anti-VEGF treatment regimens can be very effective therapies, there are a number of significant drawbacks, driven primarily by the frequency of injections that typically range from every six to eight weeks. We refer to the number of injections a patient has over a given time period as the treatment burden of the particular treatment. The actual injection at the time of administration is uncomfortable for patients and can be a deterrent in terms of compliance. Then there is the burden to both patients and their caregivers of regular office visits. These patients may not be mobile enough to travel to the office on their own and therefore require not only the assistance of a caregiver but also transportation to and from the office. Finally, while intravitreal injections are typically safe, there is the potential risk of endophthalmitis (infection in the eye), inflammation, bleeding into the vitreous gel and retinal detachment that comes with injections.

As a result of these limitations, there is a significant unmet need for technologies that will allow for a longer duration of effect and an overall reduced number of injections.

The Ocular Therapeutix Approach

Our Hydrogel-Based Formulation Technology

We apply our expertise with an established bioresorbable hydrogel-based formulation technology to the development of products for local programmed-release of known, FDA-approved therapeutic agents for a variety of ophthalmic diseases and conditions and to ophthalmic wound closure.

Our bioresorbable hydrogel-based formulation technology is based on the use of a proprietary form of PEG. Our technical capabilities include a deep understanding of the polymer chemistry of PEG-based hydrogels and the design of the highly specialized manufacturing processes required to achieve a reliable, preservative-free and pure product. We tailor the hydrogel to act as a vehicle for local programmed-release drug delivery to the eye and as an ocular tissue sealant.

We create our hydrogels by cross-linking PEG molecules to form a network that resembles a three-dimensional mesh on a molecular level. Our PEG molecules are branched, with four to eight branches or arms. Each arm bears a reactive site on its end. Our cross-linking chemistry uses a second molecule with four arms, bearing complimentary reactive sites on each end, such that when combined with the PEG molecules, a network spontaneously forms. When swollen with water, this molecular network forms a hydrogel. We design these hydrogels to slowly degrade in the presence of water, a process called hydrolysis, by inserting a biodegradable linkage between the PEG molecule and the cross-linked molecule. By appropriately selecting the number of arms of the PEG molecule and the biodegradable linkage, we can design hydrogels with varying mechanical properties and bioresorption rates. Because the body has an abundance of water at a constant temperature and pH level, hydrolysis provides a predictable and reproducible degradation rate. Our technology enables us to make hydrogels that can bioresorb over days, weeks or months.

We select the active pharmaceutical ingredients for our local programmed-release drug delivery product candidates based on criteria we have developed through our extensive experience with hydrogel-based technologies. We consider the following selection criteria:

- prior approval by the FDA for the targeted ophthalmic indication, except for our OTX-TKI program in which the active pharmaceutical ingredient, axitinib, is not currently approved for an ophthalmic indication;
- expiration of relevant patent protection prior to or within our anticipated development timeline;
- high potency to minimize required drug load in the intracanalicular insert, intracameral implant or intravitreal implant;
- availability from a qualified supplier; and

- compatibility with our drug delivery system.

We believe our current and future intracanalicular insert, intracameral implant and intravitreal implant products and product candidates may offer a range of favorable attributes as compared to eye drops and immediate release back-of-the-eye injections, including:

- *Improved patient compliance*. Our inserts and implants are placed by a healthcare professional and are designed to provide local programmed-release of drug to the ocular surface, intracameral space or intravitreal space. Because patients are not responsible for self-administration of the drug and the inserts and implants dissipate over time and do not require removal for acute conditions or frequent removal for chronic conditions, we believe our inserts and implants address the problem of patient compliance.

- *Ease of administration*. We have designed our inserts and implants to provide the entire course of medication with a single administration by a healthcare professional for acute conditions or for months for chronic conditions. We believe this avoids the need for frequent administration, reducing the patient's treatment burden and the likelihood of potential complications that could result if doses are missed.

- *Local programmed-release of drug*. We have designed our inserts and implants to deliver drug in a programmed fashion in order to avoid the peak and valley dosing and related side effects and spikes in IOP associated with eye drops, as well as current standard of care injections for the back of the eye. We also believe programmed-release dosing may improve the therapeutic profile of the active pharmaceutical ingredient because it eliminates periods of little or no drug presence between eye drop or back of the eye injection administrations. Further, we are designing our products and product candidates so that their drug release profiles can be tailored or programmed to match the treatment needs of the disease. For example, steroids for ophthalmic purposes generally require administration over four weeks, with tapered dosing over this period. In contrast, PGAs require administration in a steady fashion over the duration of treatment. Our inserts and implants are designed to fully dissipate and can be removed if necessary by a healthcare professional.

- *Avoidance of preservative side effects*. Our inserts and implants do not involve the use of preservatives, such as BAK, which have been linked to side effects including burning, stinging, hyperemia, irritation, eye dryness and, less frequently, conjunctivitis or corneal damage.

Intracanalicular Inserts

Our intracanalicular inserts, including DEXTENZA, OTX-DED, and OTX-CSI, are designed to be inserted into the patient's punctum by a healthcare professional and to release drug to the surface of the eye to address diseases including ocular inflammation and pain following ophthalmic surgery, ocular itching associated with allergic conjunctivitis, and dry eye disease.

Our intracanalicular inserts utilize our proprietary hydrogel-based formulation technology and are embedded with an active drug. Following insertion through the punctum, our inserts swell in tear fluid to fill the vertical canaliculus, which secures the inserts in place. Over time, the inserts liquefy and are cleared through the nasolacrimal duct. If necessary due to excessive tearing, discomfort or improper placement, a healthcare professional can remove an intracanalicular insert by a process of pushing the soft insert back through the punctum.

Intracameral Implants

We are engaged in the clinical development of our hydrogel administered via intracameral injection to address glaucoma. Intracameral implants refer to biodegradable or bioresorbable implants placed into the anterior chamber or front of the eye for the treatment of ocular conditions. The implants are designed to be held in place by currents and gravity present in the anterior chamber of an eye. In the case of OTX-TIC, the implant is designed to infuse with liquid, settle into the inferior angle of the eye and demonstrate little to no movement. The implants are preferably polymeric, biodegradable and provide sustained release of at least one therapeutic agent to both the trabecular meshwork and associated ocular tissue and the fluids within the anterior chamber of an eye.

Intravitreal Implants

We are engaged in the clinical development of our hydrogel administered via intravitreal injection to address the large and growing markets for diseases and conditions of the back of the eye. Our intravitreal implant product candidates, such as OTX-TKI, consist of a PEG-based hydrogel suspension, which contains embedded micronized particles of active drug. We design the intravitreal implant to be injected and retained in the vitreous humor to provide local programmed-release intravitreal delivery of anti-VEGF compounds.

Clinical Portfolio

Retinal Diseases

Age-related macular degeneration, or AMD, and diabetic retinopathy are the most common retinal diseases, affecting approximately 207.6 million and 141.2 million, respectively, worldwide, according to the Market Scope 2022 Retinal Pharmaceuticals Report. In the United States, Market Scope estimates that there are approximately 17.9 million suffering from some form of AMD.

Wet Aged-Related Macular Degeneration (Wet AMD)

Wet AMD is a serious disease of the central portion of the retina, known as the macula, an oval-shaped pigmented area that is responsible for detailed central vision and color perception. Wet AMD is characterized by abnormal new blood vessel formation, referred to as neovascularization, which results in blood vessel leakage and retinal distortion. If untreated, neovascularization in wet AMD patients typically results in formation of a scar under the macular region of the retina. The current standard of care for wet AMD is treatment with drugs that target VEGF, one of several proteins involved in neovascularization.

Wet AMD is the most common cause of visual impairment among elderly patients in developed countries. According to the Market Scope 2022 Retinal Pharmaceuticals Market Report, there are approximately 1.6 million people in the United States who suffer from wet AMD. This population is expected to grow at a 3.0% compound annual growth rate through 2027.

Diabetic Retinopathy (DR)

DR is a progressive condition in which chronically elevated levels of blood glucose and depleted levels of oxygen damage the tiny blood vessels in the retina. DR is among the most common microvascular complications of diabetes, making diabetes the leading cause of new cases of blindness in adults. DR can take time to develop. Nonproliferative DR, sometimes called background retinopathy, is usually mild and may go unnoticed. Proliferative DR is the most serious stage of the disease and develops when areas of the retina are starved for nourishment and oxygen, triggering the proliferation of new blood vessels via secretions of vascular endothelial growth factor (VEGF). The current standard of care for DR at the nonproliferative stage is watchful waiting, with the use of anti-VEGFs when the disease has progressed to the proliferative stage.

It is estimated that there were 8.4 million cases of DR in the United States in 2022 according to Market Scope, of which 3.3 million cases were moderate to severe non-proliferative DR, growing at an approximately 2% compound annual growth rate through 2027. Overall, there are an estimated 141.2 million cases of DR globally, growing at a compound annual growth rate of 3%.

Market Data

The global market for retinal disease inclusive of wet AMD and DR was approximately $15.9 billion in 2022 and is estimated to grow at approximately 6% per year through 2027 according to Market Scope. The U.S. market accounted for just over 50% of the global market or $8.5 billion in 2022 and is expected to grow at approximately 7% through 2027.

The anti-VEGF market for the treatment of wet AMD consists predominantly of three drugs that are approved for marketing and primarily prescribed for the treatment of wet AMD: Eylea, marketed in the United States by Regeneron; Lucentis, marketed in the United States by Genentech; and bevacizumab, an anti-VEGF therapy approved for the treatment of certain cancers, used off-label in ophthalmology. A new anti-VEGF, Vabysmo, launched by Genentech in 2022, has penetrated the market rapidly and is expected to gain significant market share in the future.

Retinal Disease Programs

OTX-TKI (axitinib intravitreal implant)

Our product candidate OTX-TKI is a preformed, bioresorbable hydrogel fiber implant incorporating axitinib, a small molecule TKI with anti-angiogenic properties delivered by intravitreal injection and designed for a duration of six months or longer. We are conducting a Phase 1 clinical trial in Australia and a Phase 1 clinical trial in the United States to evaluate OTX-TKI for the treatment of wet AMD. Our initial implants have delivered anti-VEGF compounds *in vitro* over a targeted nine to twelve month period, which we believe could make it possible to reduce patients' treatment burden by reducing the frequency of the current monthly or bi-monthly intravitreal injection regimen for wet AMD. We are also conducting a Phase 1 clinical trial in the United States to evaluate OTX-TKI for the treatment of DR.

We believe axitinib is well suited for use with our platform given its high potency, multi-target capability, and compatibility with a hydrogel vehicle. In the absence of a sophisticated drug delivery system, TKIs have been difficult to deliver to the eye for acceptable time frames at therapeutic levels without causing local and systemic toxicity due to low drug solubility and very short half-lives in solution. We believe our local programmed-release drug delivery technology gives us potential advantages in this regard.

We have conducted two Phase 1 trials of OTX-TKI for the treatment of wet AMD, with different formulations of axitinib. We currently intend to move forward into pivotal trials with our single 600 µg axitinib implant formulation of OTX-TKI for both the treatment of wet AMD and the treatment of diabetic retinopathy. As we have previously disclosed, we are also developing a second formulation of OTX-TKI that could be used in future trials of retinal indications. Currently, we do not believe any additional development work is required to advance to pivotal trials in either wet AMD or diabetic retinopathy.

Wet Age-Related Macular Degeneration (wet AMD)

Phase 1 Clinical Trial (Australia)

We are conducting an open-label, multi-center, proof-of-concept, dose-escalation Phase 1 clinical trial of OTX-TKI for the treatment of patients with wet AMD caused by excessive blood vessel growth in the back of the eye due to VEGF. This Phase 1 clinical trial is designed to evaluate the safety, durability and tolerability of OTX-TKI. The Phase 1 clinical trial was submitted to the Therapeutic Goods Administration, Australia's regulatory authority for therapeutic goods, in July 2018 and is being conducted at multiple sites in Australia.

Our Phase 1 clinical trial of OTX-TKI in Australia is comprised of four cohorts consisting of subjects with pre-existing intraretinal and/or subretinal fluid: a lower dose cohort of 200 µg with six subjects; a higher dose cohort of 400 µg with seven subjects; a third cohort with two parallel arms, one arm of six subjects receiving a concomitant anti-VEGF injection with 400 µg of OTX-TKI and the other arm of six subjects receiving a 600 µg of OTX-TKI with no anti-VEGF injection; and a fourth cohort with two parallel arms, one arm of six subjects receiving a 600 µg single implant of OTX-TKI and the other arm of six subjects receiving a 600 µg single implant of OTX-TKI with anti-VEGF injection. In this trial, we are evaluating whether OTX-TKI can reduce existing fluid levels. This trial's enrollment is complete. We plan to continue to follow subjects at least until their respective seventeen-month anniversaries of initial dosing, in accordance with the clinical trial protocol.

In the Phase 1 clinical trial of OTX-TKI, we are evaluating biological activity by measuring central subfield thickness, or CSFT, using spectral domain optical coherence tomography, or OCT, and following visual acuity over time as measured by Best Corrected Visual Acuity, or BCVA.

In February 2022, interim data as of January 11, 2022 from this Phase 1 clinical trial of OTX-TKI was presented at the Angiogenesis, Exudation and Degeneration Virtual Symposium. In subjects with subretinal and/or intraretinal fluid

due to wet AMD, OTX-TKI was observed to be generally well tolerated. No ocular serious adverse events were reported in treatment naïve or previously treated wet AMD subjects. Plasma concentrations of the active drug (axitinib) were measured to be below the limit of quantification of assay, or BLQ < 0.1 ng/ml, at all sampled time points for all patients in cohorts 1, 2, 3a and 3b. This assessment indicated that there was no measurable systemic exposure to axitinib.

This interim data also showed a preliminary signal of biological activity as observed by a clinically meaningful decrease in intraretinal and/or subretinal fluid as measured by high resolution OCT that provides cross-sectional images of the anatomical structure of the retina. Some subjects showed a decrease in intraretinal or subretinal fluid by two months in cohorts 2 (400 µg) and 3a (600 µg). In cohort 3b (400 µg dose plus anti-VEGF induction injection of aflibercept), two subjects showed a decrease in intraretinal or subretinal fluid as early as a week after treatment. We observed extended duration of activity of six months or more for over 60% of subjects across all cohorts and for over 80% of subjects in cohort 3a, in which we administered a 600 µg dose.

In addition, the OTX-TKI implants in cohort 1 (single implant) were observed to have biodegraded in all subjects within nine to 10.5 months of injection. It has also been observed in the trial that the implants were able to be adequately monitored and that there was limited to no movement of the implant in the anterior segment of the eye.

Phase 1 Clinical Trial (United States)

In July 2021, we announced that we had dosed the first patient in a prospective, multi-center, randomized, controlled Phase 1 clinical trial in the United States under an exploratory investigational new drug, or eIND, application to evaluate a single implant 600 µg dose of OTX-TKI with an anti-VEGF injection in comparison with a 2 mg dose of aflibercept. The population we are studying in this U.S.-based clinical trial is different than the population we are studying in our ongoing Phase 1 clinical trial of OTX-TKI in Australia. In this trial, we are evaluating how long we are able to maintain subjects who have been previously treated with anti-VEGF therapy without the need for retreatment.

The trial enrolled a total of 21 subjects at six clinical sites, comprising two arms consisting of subjects previously treated with, and responsive to, standard of care anti-VEGF therapy: a 16-subject arm receiving OTX-TKI in combination with a single anti-VEGF injection at month one and a five-subject arm receiving on-label aflibercept at eight-week intervals. The trial is designed to assess the safety, durability and tolerability of OTX-TKI as well as to assess preliminary biological activity in subjects by measuring anatomical and functional changes. This trial was fully enrolled as of February 2022.

In February 2023, we announced interim 10-month data from the ongoing Phase 1 clinical trial of OTX-TKI in the United States at the Angiogenesis, Exudation, and Degeneration 2023 Annual Meeting. As of the December 12, 2022 cut-off date, the interim data showed that the single 600 µg OTX-TKI implant was generally well tolerated with no drug-related ocular or systemic serious adverse events, or SAEs, observed through 10 months. One SAE of endophthalmitis was observed in the OTX-TKI arm which occurred following the aflibercept injection required by the clinical trial protocol at month one and was assessed by the investigator as related to the injection procedure. There were no instances of elevated IOP, retinal detachment, retinal vasculitis, or implant migration into the anterior chamber observed in the OTX-TKI arm, and no subjects had dropped out of either arm as of the data cutoff.

The interim results showed subjects treated with a single OTX-TKI implant demonstrated stable and sustained BCVA (mean change from baseline of -0.3 letters) and CSFT (mean change from baseline of -1.3 µm) in the OTX-TKI arm at 10 months, which was comparable with the aflibercept arm (mean change from BCVA baseline of -0.8 letters; mean change from CSFT baseline of -4.5 µm). Up to Month 10, 73% of subjects remained rescue-free. Overall, a 92% reduction in treatment burden (average percent decrease in injections over the period compared to a standard monthly injection regimen) was observed in OTX-TKI treated subjects for up to 10 months. Four subjects were rescued in the OTX-TKI arm up to Month 10. One subject, the subject who experienced endophthalmitis, was rescued twice. None of these rescues met the preestablished rescue criteria set forth in the clinical trial protocol and were instead initiated at investigator discretion. One additional subject, who met the established rescue criteria at such subject's Month 10 visit, was rescued at the end of Month 10.

There was one subject randomized to the OTX-TKI arm who was inadvertently given aflibercept instead of sham injections at the subject's month three and month five visits. Since this subject was not treated according to protocol, the subject was excluded from the analysis of biological activity, which comprised 15 out of the 16 subjects in the OTX-TKI

arm and all five subjects in the aflibercept arm, but the subject was included in the safety analysis which comprised all 16 subjects in the OTX-TKI arm and all five subjects in the aflibercept arm.

Per protocol, we will continue to follow subjects in the Phase 1 trial at least until their respective one-year anniversaries of initial dosing.

Regulatory Pathway

We are in active discussions with the FDA regarding the regulatory pathway for OTX-TKI for the treatment of wet AMD and potential future clinical trial requirements. Subject to those discussions and obtaining the necessary financing, which could be provided through a strategic alliance, we aim to be prepared to initiate a pivotal clinical trial for the treatment of wet AMD in the third quarter of 2023. If we were to obtain favorable results from two pivotal clinical trials, we expect that we would submit an NDA under Section 505(b)(2) of the FDCA. See "—Government Regulation—Section 505(b)(2) NDAs" for additional information.

Diabetic Retinopathy (DR)

Phase 1 Clinical Trial

Given our belief in the potential applicability of OTX-TKI to other retinal diseases, we initiated a Phase 1 U.S.-based clinical trial to evaluate OTX-TKI for the treatment of DR in the fourth quarter of 2022 and dosed our first patient in February 2023. We are conducting the Phase 1 clinical trial initially under an eIND. The trial is designed to include approximately 21 subjects with diabetic retinopathy secondary to type 1 or type 2 diabetes who had not had an anti-VEGF injection in the prior 12 months or DME in the prior six months, randomized 2:1 to either a single 600 μg implant of OTX-TKI or sham control across approximately 10 sites. We anticipate disclosing topline results as early as the fourth quarter of 2023.

Regulatory Pathway

We are in active discussions with the FDA regarding the clinical development of OTX-TKI. Assuming positive topline data results from the Phase 1 clinical trial, the finalization of the design of our clinical development program reflecting of our ongoing discussions with the FDA, and additional financing to fund the trials, we believe we could be in a position to initiate our first pivotal trial of OTX-TKI for the treatment of DR as early as the first quarter of 2024 and a second pivotal trial shortly thereafter. If we were to obtain favorable results from these two pivotal clinical trials, we expect that we would submit an NDA under Section 505(b)(2) of the FDCA. See "—Government Regulation—Section 505(b)(2) NDAs" for additional information.

Glaucoma

Glaucoma is a progressive and highly individualized disease in which elevated levels of IOP are associated with damage to the optic nerve, which results in irreversible vision loss. According to the World Health Organization, glaucoma is the second leading cause of blindness in the world. Ocular hypertension is characterized by elevated levels of IOP without any optic nerve damage. Patients with ocular hypertension are at high risk of developing glaucoma.

In a healthy eye, fluid is continuously produced and drained to maintain pressure equilibrium and provide nutrients to the ocular tissue. Excess fluid production or insufficient drainage of fluid in the front of the eye or a combination of these problems causes increased IOP. The increased IOP associated with uncontrolled glaucoma results in degeneration of the optic nerve in the back of the eye and loss of peripheral vision. Once glaucoma develops, it is a chronic condition that requires life-long treatment.

According to Market Scope, it is estimated that there were 172.0 million people globally in 2023 with primary open-angle glaucoma or ocular hypertension. In the United States, it is estimated there are 6.8 million and 3.7 million who had primary open-angle glaucoma or ocular hypertension, respectively. Both groups are estimated to grow by 1.3% and 2.4% annually through 2026, respectively. The primary goal of glaucoma treatment is to slow the progression of this chronic disease by reducing IOP, and many medications can accomplish this. Importantly, however, adherence to current topical glaucoma therapies is known to be particularly poor with reported rates of non-adherence from 30% to

80%. These low compliance rates may be associated with disease progression and loss of vision and may be part of the reason that glaucoma is a leading cause of blindness in people over 60 years of age. Prostaglandins are the most commonly used class of medications to treat patients with glaucoma and are administered via daily eye drops as the current standard of care. The ability of patients to use and place daily eye drops is challenging. The product candidates that we are developing are designed to address the issue of compliance by delivering a prostaglandin analog, or PGA, formulated with our programmed release hydrogel to lower IOP for several months with a single insert.

Market Data

The global market for glaucoma was estimated by Market Scope at $4.3 billion in 2023 with the U.S. market representing $1.6 billion. The global market is estimated to grow at 5.1% annually to approximately $5.5 billion in 2028 while the U.S. market is expected to grow 3.5% annually to approximately $1.9 billion in 2026.

The market for drugs administered by eye drops for the treatment of glaucoma consists of both branded and generic products. Branded products have maintained premium pricing and significant market share. These products include Lumigan (bimatoprost) marketed by Allergan, Travatan Z (travoprost) marketed by Novartis and Tapros marketed by Santen. Commonly used generic drugs include latanoprost and timolol.

Glaucoma Program

OTX-TIC (travoprost intracameral implant)

Our product candidate OTX-TIC is a bioresorbable hydrogel implant incorporating travoprost, an FDA-approved prostaglandin analog designed to lower elevated IOP, that is designed to be administered by a physician as an intracameral injection with an initial target duration of drug release of four to six months with a single treatment.

Phase 1 clinical development

We submitted an IND for OTX-TIC in February 2018 and have completed a prospective, multi-center, open-label, dose-escalation, proof-of-concept Phase 1 clinical trial of OTX-TIC in the United States that we initiated in the second quarter of 2018 for the treatment of subjects with moderate to severe glaucoma or ocular hypertension. The clinical trial is designed to evaluate the safety, biological activity, durability and tolerability of OTX-TIC in subjects with controlled open-angle glaucoma or ocular hypertension. The clinical trial consisted of four patient cohorts: cohort 1 included five subjects who received a 15 µg dose, cohort 2 included four subjects who received a 26 µg dose, cohort 3 included five subjects who received a 15 µg dose with a fast-degrading implant, and cohort 4 included five subjects who received a 5 µg dose with a fast-degrading implant.

In February 2022, at the Glaucoma 360 virtual meeting, we presented interim results from all four subject cohorts in the Phase 1 clinical trial. We believe, based on these results, that OTX-TIC shows potential as a sustained-release therapy with a long duration of action. In the Phase 1 clinical trial, at least one subject in each of the four cohorts receiving OTX-TIC were observed to experience a mean change in IOP from baseline as measured at 8:00 am, 10:00 a.m. and 4:00 p.m. as early as two days following injection. We believe these results were comparable to the decrease in IOP achieved with topical travoprost administered via daily eye drops, the current standard of care. IOP lowering effects lasted more than six months in subjects in cohorts 1 and 2 and three to six months in subjects in cohorts 3 and 4.

The OTX-TIC implant was observed to biodegrade in between five and seven months in subjects in cohorts 1 and 2. In subjects in cohorts 3 and 4, the fast-degrading implants biodegraded between three and five months. Within all four cohorts, implants were not observed to move when viewed with a slit lamp biomicroscope and were visible at all examinations in all subjects using gonioscopy. Corneal health as measured by endothelial cell counts, pachymetry assessments, and slit lamp examinations did not indicate any clinically meaningful changes from baseline in any of the four cohorts. IOP elevation was observed in three subjects in cohort 3 at the approximate time of the implant resorption.

Phase 2 Clinical Trial

We are conducting a U.S.-based Phase 2 prospective, multi-center, randomized, controlled clinical trial evaluating the safety, tolerability and efficacy of OTX-TIC for the treatment of patients with primary open-angle glaucoma or ocular hypertension. The Phase 2 clinical trial was designed to include approximately 105 subjects at 15 to 20 sites

between three arms of approximately 35 subjects each to evaluate two formulations of OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension in subjects compared to DURYSTA. The non-study eye of each subject will receive a topical prostaglandin daily. The primary efficacy endpoint is measured by diurnal IOP mean change from baseline (8 a.m., 10 a.m. and 4 p.m.) at two, six and 12 weeks. The active comparator control arm will receive one injection of DURYSTA in one eye and a topical prostaglandin daily in the non-study eye.

We initiated the Phase 2 clinical trial in the fourth quarter of 2021 and dosed the first subject in the first quarter of 2022. One arm in the Phase 2 clinical trial is receiving the same formulation used in cohort 2 of the Phase 1 clinical trial, containing a 26 µg dose of drug and utilizing a standard implant. The second arm was receiving the same formulation used in cohort 4 of the Phase 1 clinical trial, containing a 5 µg dose of drug and utilizing a fast-degrading implant. Due to elevations in IOP observed approximately 12 weeks after enrollment in six subjects in the OTX-TIC 5 µg arm of the trial, we terminated enrollment in the 5 µg arm of the trial in the fourth quarter of 2022 and are continuing forward with the OTX-TIC 26 µg and DURYSTA arms of the trial. We expect that the Phase 2 clinical trial will consist of approximately 86 patients: approximately 35 patients in the OTX-TIC 26 µg treatment arm, 35 patients in the DURYSTA arm and approximately 16 patients that were previously enrolled in the OTX-TIC 5 µg treatment arm. Enrollment is ongoing. We plan to provide topline data from the trial in the fourth quarter of 2023.

Regulatory Pathway

If our Phase 2 clinical trial is successful and subject to obtaining the necessary financing, we would then be required to successfully complete two well-controlled pivotal clinical trials conducted under an IND to obtain marketing approval from the FDA. If we were to obtain favorable results from these two pivotal clinical trials, we expect that we would submit an NDA to the FDA for marketing approval of OTX-TIC under Section 505(b)(2) of the FDCA. See "—Government Regulation—Section 505(b)(2) NDAs."

Ocular Surface Diseases

Dry Eye Disease

Dry eye disease is a chronic, multifactorial disease affecting the tears and ocular surface that can result in dryness, inflammation, irritation, pain, tear film instability, visual disturbance and ocular surface damage. Dry eye disease can have a significant impact on quality of life and can potentially cause long-term damage to the ocular surface. Due to the impact of dry eye disease on tear film dynamics, the condition can affect performance of common vision-related activities such as reading, using a computer and driving, and can lead to complications associated with visual impairment. In addition, the vast majority of dry eye patients experience acute episodic exacerbations of their symptoms, which are commonly referred to as flares, at various times throughout the year. These flares can be triggered by numerous factors, including exposure to allergens, pollution, wind and low humidity, intense visual concentration such as watching television and working at a computer, hormonal changes, contact lens wear, smoking and sleep deprivation, which cause ocular surface inflammation and impact tear production and/or tear film stability.

There are approximately 17.8 million patients diagnosed with dry eye disease in the United States, according to the Market Scope 2022 Dry Eye Products Market Report. Approximately 9.8 million of those patients are diagnosed with moderate to severe dry eye while the remaining 8.0 million patients are diagnosed with mild dry eye disease. The prevalence of dry eye disease increases with age, and we expect that the number of dry eye disease cases will increase as the U.S. population continues to age.

The current standard of care for moderate to severe dry eye disease is the use of artificial tears and topical anti-inflammatory and immune modulating drugs administered by prescription eye drops. The anti-inflammatory and immune modulating prescription drug market consists of Restasis, for increasing tear production, marketed by Allergan; Cequa for increasing tear production, marketed by Sun Ophthalmics in the United States; lifitegrast, for the treatment of the signs and symptoms of dry eye disease, marketed by Novartis under the brand name Xiidra; and off-label use of corticosteroids. As each of Restasis and Xiidra have a relatively long onset of action, they are not generally used for the short-term treatment of episodic dry eye flares. In addition, patients have reported significant issues with stinging and burning when using several of the current treatments.

Market Data

The global market for dry ocular surface disease, which we refer to as dry eye disease, was estimated by Market Scope at $5.7 billion in 2022 with the U.S. market representing $2.2 billion. There are many products to treat dry eye on the market from over an estimated 150 companies, from both the pharmaceutical and OTC segments. Within the prescription category, two of the better-known branded products are Xiidra® from Novartis and Restasis from Allergan. In 2022, Xiidra recorded global sales of $487 million while Restasis recorded sales of $666 million.

Post-Surgical Ocular Inflammation and Pain

Ocular inflammation and pain are common side effects following ophthalmic surgery. Frequently performed ophthalmic surgeries include cataract, refractive, vitreoretinal, cornea, and glaucoma procedures. Physicians prescribe anti-inflammatory drugs, such as corticosteroids, which are typically administered through eye drops multiple times per day, following ocular surgery as the standard of care. These drugs improve patient comfort and also accelerate recovery through disruption of the inflammatory cascade resulting in decreased inflammation and reduced activity of the immune system. Physicians also frequently prescribe non-steroidal anti-inflammatory drugs, or NSAIDs, as adjunctive or combination therapy to supplement the use of corticosteroids. If left untreated, inflammation of the eye may result in further ocular complications, including pain, scarring and vision loss.

Market Data

Market Scope has estimated that approximately 4.7 million ocular surgeries were performed in the United States in 2022, an increase of approximately 3.3% over 2021. Market Scope further estimates that approximately 4.6 million are estimated to have been cataract surgeries, an increase of 3.1% over 2021. We currently focus our sales efforts for DEXTENZA for the treatment of inflammation and pain on patients covered by Medicare Part B which accounts for roughly 50% of all cataract surgeries or approximately 2 million surgeries annually. At the current wholesale acquisition price of $555 per insert, we estimate that there is a near-term addressable market of approximately $1 billion per year in the surgical space.

According to IQVIA, Inc. data, approximately 20.4 million prescriptions were filled in the United States in 2022 for anti-inflammatory drugs administered by prescription eye drops for ocular diseases and conditions, resulting in sales of approximately $4.9 billion. These prescriptions consisted of approximately 8.5 million prescriptions and $581.1 million in sales for single-agent corticosteroids, 3.2 million prescriptions and $285.5 million in sales for NSAIDs, 4.7 million prescriptions and $356.2 million in sales for corticosteroid and antibiotic combination products and approximately 4.4 million prescriptions and $3.7 billion in sales for dry eye disease products.

Allergic Conjunctivitis

Allergic conjunctivitis, another ocular surface disease, is an inflammatory disease of the conjunctiva resulting primarily from a reaction to allergy-causing substances such as pollen or pet dander. The primary sign of this inflammation is redness and the primary symptom is acute itching. Allergic conjunctivitis ranges in clinical severity from relatively mild, common forms to more severe forms that can cause impaired vision. According to a study on the management of seasonal allergic conjunctivitis published in 2012 in the peer-reviewed journal *Acta Ophthalmologica*, allergic conjunctivitis affects 15% to 40% of the U.S. population. The first line of defense against allergic conjunctivitis is avoidance of the allergen. If this is not successful, physicians typically prescribe a combination of a topical mast cell stabilizer and an anti-histamine. These treatments act to reduce the signs and symptoms of the early phase allergic reaction. For the subset of patients with chronic or more severe forms of allergic conjunctivitis, anti-histamines and mast cell stabilizers are often not sufficient to treat their signs and symptoms. These refractory patients are frequently treated with topical corticosteroids administered by prescription eye drops.

It is estimated that up to 10 million people in the United States seek medical attention annually for the inflammatory response associated with allergic conjunctivitis caused by both seasonal and perennial allergens.

Market Data

According to IQVIA, Inc. data, approximately 4.5 million anti-allergy eye drop prescriptions were filled in the United States in 2022, resulting in sales of approximately $255.5 million. The market to treat allergic conjunctivitis

consists of antihistamines, mast-cell stabilizers and steroid eye drops and consists of both branded and generic products. Branded steroids include Lotemax and Alrex (loteprednol etabonate) marketed by Bausch & Lomb, and Durezol (difluprednate) marketed by Alcon. Commonly used generic steroids include prednisolone, dexamethasone and fluorometholone.

Ocular Surface Disease Programs

We are engaged in the development of formulations of our hydrogel administered via intracanalicular inserts to address large markets for diseases and conditions of the surface of the eye. Our initial development efforts are focused on the use of our extended-delivery hydrogel in combination with well-known and well-understood drugs (corticosteroids and cyclosporine) for the treatment of dry eye disease, allergic conjunctivitis and inflammation and pain following ophthalmic surgery.

Dry Eye Disease Program

OTX-DED (dexamethasone intracanalicular insert)

One of the causes of dry eye disease is inflammation. Topical anti-inflammatory drugs are used as one of several therapies to treat dry eye disease and are administered by eye drops. As the understanding of dry eye disease, specifically the inflammatory components of dry eye disease, has evolved, the use of corticosteroids has become common to offer short-term relief of signs and symptoms of the disease. Physicians typically prescribe a topical corticosteroid for a period of two to four weeks, tapered over the course of delivery as the inflammation and symptoms subside. However, safety limitations associated with the prolonged use of corticosteroids for dry eye disease have limited widespread adoption. We believe that OTX-DED has potential as a short-term treatment of the signs and symptoms of dry eye disease caused by inflammation.

Our product candidate OTX-DED incorporates the FDA-approved corticosteroid dexamethasone as a preservative-free active pharmaceutical ingredient in a hydrogel, drug-eluting intracanalicular insert. OTX-DED incorporates the same active drug as DEXTENZA but includes a lower dose of the drug, is administered in the office setting as a smaller insert and is designed to release dexamethasone over a period of two to three weeks, compared with up to thirty days in the case of DEXTENZA.

Phase 2 clinical trial

We submitted an IND in November 2020 for OTX-DED. In February 2021, we initiated a U.S.-based, randomized, double-masked, vehicle-controlled, multi-center Phase 2 clinical trial evaluating two different-strength formulations of OTX-DED (0.2 mg and 0.3 mg of dexamethasone) versus a hydrogel implant in a total of 166 subjects with dry eye disease, with more than 50 subjects per arm. The subjects were followed for approximately two months after randomization. This trial was designed to assess the safety and efficacy of these two formulations of OTX-DED for the short-term treatment of signs and symptoms of dry eye disease. Included subjects were required to have diagnosed dry eye disease in both eyes for at least six months, a Visual Analog Score, or VAS, eye dryness severity score of at least 30 and bulbar conjunctival hyperemia grade of at least 2 on the Cornea Contact Lens Research Unit (CCLRU) Grading scale. The primary endpoint was mean change in bulbar conjunctival hyperemia from baseline measured at 15 days post treatment by central reading center photographic assessment. Secondary endpoints included eye dryness symptoms using VAS, total CFS, or corneal total fluorescein staining, using the National Eye Institute scale and adverse events, both ocular and non-ocular.

We announced the topline Phase 2 clinical results in December 2021. The clinical trial achieved its pre-specified primary endpoint. Although the clinical trial was not powered to show statistical significance, the topline results demonstrated a statistically significant change of bulbar conjunctival hyperemia from baseline to day 15 compared to the vehicle hydrogel using a central reading photographic assessment in the modified ITT population. Change from baseline using the CCLRU Grading scale (0-4) was -0.51 for the OTX-DED 0.2 mg group (n=55), -0.43 for the OTX-DED 0.3 mg group (n=56), and -0.21 for the vehicle hydrogel insert group (n=55). These differences were statistically significant compared with the vehicle hydrogel for both the OTX-DED 0.2 mg group (p=.004) and the OTX-DED 0.3 mg group (p=.028). Sensitivity analysis using different methods of imputation including last observation carry forward (LOCF), Markov Chain Monte Carlo (MCMC), and fully conditioned specifications (FCS) were consistent with the primary

analysis. Improvements from baseline were noted in the VAS dry eye symptoms for both OTX-DED 0.2 mg and OTX-DED 0.3 mg groups, but there was little separation between OTX-DED and the vehicle hydrogel insert.

Both formulations of OTX-DED were generally observed to have a favorable safety profile and be well tolerated. There were no ocular serious adverse events observed. The most common ocular adverse events for subjects treated with OTX-DED were epiphora (lacrimation increase) (8.1%) and elevated IOP (3.6%). All other ocular adverse events occurred in less than 1% of subjects. The most common non-ocular adverse event for subjects treated with OTX-DED was arthralgia (joint pain) which was seen in 1.8% of subjects. All other non-ocular adverse events occurred in less than 1% of subjects.

Regulatory Pathway

Based on the data from the Phase 2 clinical trial, we intend to conduct a small trial in connection with our efforts to develop an appropriate placebo comparator that may be used in both the OTX-DED and OTX-CSI programs. Specifically, we intend to evaluate the performance of OTX-DED versus placebo inserts, namely fast-dissolving, biodegradable collagen plugs, and no inserts at all, to explain the placebo performance seen in the Phase 2 clinical trials evaluating both OTX-DED and OTX-CSI in which the vehicle hydrogel placebo insert or placebo comparator vehicle remained in the canaliculus longer than anticipated, performing more like an active comparator than a placebo. We currently expect to begin this trial in the first half of 2023.

If we determine to advance the program, we believe we could advance the program to pivotal trials subject to a discussion with the FDA. We would then be required to successfully complete two well-controlled Phase 3 clinical trials conducted under an IND to obtain marketing approval from the FDA. If our development efforts are successful, we expect that we would submit an NDA under Section 505(b)(2) of the FDCA. See "—Government Regulation—Section 505(b)(2) NDAs" for additional information.

OTX-CSI (cyclosporine intracanalicular insert)

OTX-CSI incorporates the FDA-approved immunomodulator cyclosporine as a preservative-free active pharmaceutical ingredient into a hydrogel, drug-eluting, intracanalicular insert. The product candidate is designed for subjects suffering from moderate to severe dry eye and to be administered by a physician as a bioresorbable intracanalicular insert. OTX-CSI is designed to release cyclosporine to the ocular surface for approximately three to four months in order to increase tear production for the chronic treatment of dry eye disease.

Phase 1 clinical development

We submitted an IND for OTX-CSI in the United States in December 2019 and initiated a Phase 1 clinical trial in the first quarter of 2020. The Phase 1 clinical trial was a U.S.-based, open-label, single-center trial that included five subjects (ten eyes) who were followed for approximately four months. The study was designed to evaluate the safety, tolerability and durability of OTX-CSI and assess the biological activity by measuring signs and symptoms of dry eye disease over this time period.

On October 8, 2020, we announced topline data from our Phase 1 clinical trial evaluating OTX-CSI in the chronic treatment of dry eye disease. All subjects completed the 16-week study period with no drop-outs. There were no serious adverse effects reported. The inserts were observed to be well-tolerated, and there were no adverse events of stinging, irritation, blurred vision or tearing reported or observed.

Tear production as measured by the Schirmer's test improved from mean values of 4.2 mm at baseline to 8.2 mm at Week 12. One of five subjects (20%) had a greater than 10 mm increase from baseline in Schirmer's score at Week 12. Subjects saw an improvement in signs of dry eye disease as measured by CFS (a mean value of 6.7 at baseline, improved to a mean value of 2.7 at Week 12, on a scale of 0 to 15). Further, subjects saw an improvement in symptoms of dry eye disease as measured by the VAS eye dryness severity score (a mean value of 51 at baseline, improved to a mean value of 33 at Week 12, on a scale of 0 to 100) and the VAS dry eye frequency score (a mean value of 51 at baseline, improved to a mean value of 31 at Week 12, on a scale of 0 to 100). The onset of action of OTX-CSI was seen as early as two weeks for both signs and symptoms of dry eye disease and was observed to continue over the sixteen-week study period.

Phase 2 clinical development

In September 2020, we dosed the first subjects in a U.S.-based, randomized, double-masked, multi-center, vehicle-controlled Phase 2 clinical trial designed to assess the safety, tolerability and durability and to evaluate the efficacy of OTX-CSI in the chronic treatment of dry eye disease. The Phase 2 clinical trial evaluated two different formulations of OTX-CSI compared with a hydrogel vehicle insert in approximately 140 subjects who were followed for a period of 16 weeks (12-week study period, with an additional 4-week safety follow-up). Included subjects must have been diagnosed with dry eye disease in both eyes for a period of greater than six months and have a VAS eye dryness severity score of greater than 30. The primary endpoints are incidence of treatment-emergent adverse events and the absolute value and change from baseline at week 12 in tear production as measured by the Schirmer's test. Secondary endpoints include signs of dry eye disease as measured by CFS and symptoms of dry eye disease as measured by the VAS eye dryness severity score and the VAS dry eye frequency score.

We announced topline results from our Phase 2 clinical trial in October 2021. In the Phase 2 clinical trial, OTX-CSI was administered to 147 subjects with dry eye disease at 15 sites in the United States. The four groups evaluated in this study were: OTX-CSI for a shorter duration (two to three months formulation-F1, n=42), OTX-CSI for a longer duration (three to four months formulation-F2a, n=40), vehicle insert for a longer duration (three to four months formulation-F2b, n=43) and vehicle insert for a very short duration (one week formulation-F3, n=22).

The study did not show separation between subjects receiving OTX-CSI (both formulations) and subjects receiving the vehicle (both formulations) for the primary endpoint of increased tear production at 12 weeks as measured by the Schirmer's Test. Mean change from baseline (improvement) in Schirmer's Test scores for the four groups were as follows: OTX-CSI F1: 1.98 mm, OTX-CSI F2a: 1.91 mm, Vehicle F2b: 2.24 mm and Vehicle F3: 3.08 mm.

The study did show an improvement compared with baseline in signs of dry eye disease as measured by total CFS and symptoms of dry eye disease as measured by the VAS eye dryness in subjects treated with the OTX-CSI insert (both formulations) starting as early as two weeks after insertion and continuing over the 12 weeks study period. These improvements were not statistically significant compared with vehicle insert (both formulations) for either CFS or VAS eye dryness (severity and frequency) at 12 weeks.

Overall, the OTX-CSI insert (both formulations) was generally observed to have a favorable safety profile and be well tolerated. There were no ocular serious adverse events observed. No subjects dropped out of the trial due to an adverse event. The most common ocular adverse event was ocular pruritis, or itchy eyes, which was seen in less than 16% of subjects. The adverse events of ocular discomfort or pain were seen in less than 3% of subjects. The most common non-ocular event was COVID-19 and was seen in 3% of subjects.

Regulatory Pathway

We are continuing formulation work to extend the durability of the OTX-CSI insert and select the most appropriate formulations to move forward. If we determine to advance the program, we believe we could advance the program to pivotal trials subject to discussions with the FDA. We would then be required to successfully complete two well-controlled pivotal clinical trials conducted under an IND to obtain marketing approval from the FDA. If our development efforts are successful, we expect that we would submit an NDA under Section 505(b)(2) of the FDCA. See "—Government Regulation—Section 505(b)(2) NDAs" for additional information.

Additional Potential Areas for Growth

We continue to leverage the potential of our hydrogel platform to explore areas for growth with a focus on formulating, developing and commercializing innovative therapies for diseases and conditions of the eye.

Complement Inhibitor. In June 2021, we entered into an agreement with Mosaic Biosciences, Inc., or Mosaic, to identify new targets and discover novel therapeutic agents aimed at the treatment of dry AMD. Dry AMD can progress to an advanced condition known as geographic atrophy, or GA. Vision loss from GA is typically more gradual than it is from wet AMD. In its 2022 Retinal Pharmaceuticals Market Report, Market Scope estimated that there are 1.6 million people with GA in the United States and more than 13 million globally, both growing at an estimated compound annual growth rate of 3%.

Our collaboration with Mosaic has yielded lead compounds that Mosaic has humanized and is now optimizing for our preclinical complement inhibitor program. We believe that product candidates with these compounds have the potential for targeted dosing of every three to four months.

Companies actively pursuing treatments for GA through the inhibition of the complement system include Apellis Pharmaceuticals, Inc. and Iveric bio, Inc. Apellis' Syfovre received marketing approval from the FDA in February of 2023. In February 2023, Iveric Bio, Inc. also announced that the FDA had accepted the company's NDA for avacincaptad pegol for filing and established a PDUFA target action date in August 2023. We are aware that several other companies are actively developing product candidates for the treatment of GA, including Annexon Biosciences, Inc. Novartis Ionis (in collaboration with Roche/Genentech), AstraZeneca, The Janssen Pharmaceutical Companies of Johnson & Johnson (after acquisition from Hemera Biosciences), Alkeus Pharmaceuticals, Inc., Lineage Cell Therapeutics, Inc. (in collaboration with Roche/Genentech), and Regenerative Patch Technologies, LLC.

Gene Delivery Program. We have a preclinical program using our hydrogel technology to control the release of vectors such as AAV to ocular tissues for the treatment of inherited and acquired ocular diseases, including dry or wet AMD. We believe that our hydrogel formulation technology may be uniquely suited to deliver a gene therapy safely, effectively and efficiently with a longer duration of effect. Companies actively pursuing gene therapy to address ocular diseases and conditions of the eye include Adverum Biotechnologies, GenSight, REGENXBIO, and Spark Therapeutics.

Commercial Portfolio

Post-Surgical Ocular Inflammation and Pain

DEXTENZA (dexamethasone intracanalicular insert)

DEXTENZA incorporates the FDA-approved corticosteroid dexamethasone as a preservative-free active pharmaceutical ingredient into a hydrogel, drug-eluting intracanalicular insert. Following FDA approval, we commercially launched DEXTENZA for the treatment of post-surgical inflammation and pain in July 2019. DEXTENZA is the first FDA-approved intracanalicular insert delivering dexamethasone to treat post-surgical ocular inflammation and pain for up to 30 days with a single administration.

We selected dexamethasone as the active pharmaceutical ingredient for DEXTENZA because it is approved by the FDA and has a long history of ophthalmic use; is available on a generic basis; is highly potent and is typically prescribed for prevention of ocular inflammation and pain following ocular surgery; is available from multiple qualified suppliers; and has physical properties that are well suited for incorporation within our hydrogel technology.

The dexamethasone drug particles embedded within our DEXTENZA intracanalicular insert gradually erode and release the drug in a programmed fashion until the drug is depleted. As the dexamethasone drug particles erode and the hydrogel degrades by hydrolysis, the intracanalicular insert softens, liquefies and is cleared through the nasolacrimal duct. We provide the DEXTENZA drug product in a preservative-free formulation in a sterile, single use package.

The standard regimen for dexamethasone eye drops following cataract surgery is an initial administration of four times daily for one week, with a gradual tapering in the number of eye drops over a four-week period. Such a regimen is often confusing to patients as they must remember to taper the number of times per day they administer the steroid, while also taking multiple drops of other drugs, such as antibiotics and NSAIDs. We believe that local programmed-release of drug to the eye may result in better control of ocular inflammation and pain as compared to prescription eye drops and that a low dose amount may provide enhanced safety by eliminating spikes in IOP associated with high-dose steroid eye drops.

Investigator-Initiated Trials

We have received proposals for, and are supporting, several investigator-initiated trials evaluating DEXTENZA in different clinical situations. To date, third-party clinical investigators have initiated over 45 trials to study the use of DEXTENZA in cataract surgery, other ophthalmic surgeries and other potential indications. Over 25 of the trials have completed enrollment, and the remaining trials are actively enrolling and treated subjects are being followed.

Post-Approval Studies

In September 2020, we announced that we had dosed the first pediatric subjects in a U.S.-based, randomized, multicenter Phase 3 clinical trial evaluating DEXTENZA for the treatment of post-surgical ocular inflammation and pain in children following cataract surgery. This clinical trial is a post-approval requirement of the FDA in accordance with the Pediatric Research Equity Act of 2003, in connection with the FDA's prior approval of DEXTENZA for the treatment of inflammation and pain following ophthalmic surgery in adults. We intend to enroll approximately 60 subjects in this clinical trial. It is designed to evaluate the safety and biological activity of DEXTENZA compared to an active control, prednisolone acetate suspension eye drops, for the treatment of inflammation and pain following ocular surgery for pediatric cataract in children between zero and three years of age. The primary endpoint is the absence of pain at day eight post-treatment as measured by a FLACC (Face, Legs, Activity, Cry, Consolability) score of zero. Enrollment is ongoing. The FDA has agreed that this Phase 3 clinical trial evaluating DEXTENZA for the treatment of post-surgical ocular inflammation and pain in children following cataract surgery may also satisfy the post-approval requirement for a pediatric trial as it relates to indication ocular itching associated with allergic conjunctivitis.

Foreign Approvals

Outside the United States, we continue to assess whether to seek regulatory approval for DEXTENZA in markets such as the European Union, Australia and Japan based on the market opportunity, particularly pricing, and the requirements for marketing approval. Given our prioritization of the clinical development of our sustained-release product candidates and our planned commercialization efforts for our initial intracanalicular insert product candidates in the United States, we will need to engage third parties to assist us in the approval process.

We have entered into a license agreement and collaboration with AffaMed for the development and commercialization of DEXTENZA, along with OTX-TIC, in specified Asian markets. In January 2022, AffaMed dosed its first subject in a study conducted in China evaluating the safety and efficacy of DEXTENZA for the treatment of ocular inflammation and pain post-cataract surgery. This prospective, single-arm, real-world trial is designed to assess the safety and efficacy of DEXTENZA for the treatment of ocular inflammation and pain following cataract surgery in approximately 120 patients at the Bo'ao Super Hospital. The trial's primary efficacy endpoint is the absence of anterior chamber cells in the study eye at Day 14, and the key secondary endpoint is the absence of pain in the study eye at Day 8. In April 2022, AffaMed announced that DEXTENZA has been approved in Macau, China for the treatment of ocular inflammation and pain following ophthalmic surgery. We do not expect that DEXTENZA sales in Macau will result in material revenues to us.

We retain the right to develop and commercialize DEXTENZA in all other global markets. From time to time, we may consider additional arrangements with other companies to address markets outside of the United States. If we or our collaborators obtain regulatory approval to market and sell DEXTENZA in international markets, we expect to utilize a variety of types of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize DEXTENZA. See "—Government Regulation—Review and Approval of Medical Devices in the European Union" for additional information.

Allergic Conjunctivitis

DEXTENZA (dexamethasone ophthalmic insert) for the Treatment of Ocular Itching Associated with Allergic Conjunctivitis

In October 2021, the FDA approved our sNDA, for DEXTENZA to include the treatment of ocular itching associated with allergic conjunctivitis as an additional indication. With the approval, DEXTENZA became the first, FDA-approved, physician-administered intracanalicular insert capable of delivering a preservative-free drug for the treatment of ocular itching associated with allergic conjunctivitis with a single administration for up to 30 days. DEXTENZA for the treatment of ocular itching associated with allergic conjunctivitis also represents our first indication approved to be administered in a physician's office during a routine, non-surgical appointment.

Although dexamethasone is clinically effective in the treatment of late-phase inflammatory allergic reactions, the safety limitations associated with eye drop administration, including the potential to generate spikes in IOP due to the high levels of drug due to potential patient abuse to treat this symptomatic condition, have limited its widespread adoption. These elevations in IOP can lead to drug-induced glaucoma, although the incidence is low. Further, use of oral

antihistamine medications as well as anti-histamine eye drops for allergic conjunctivitis may dry out the eye and exacerbate the discomfort to some patients. Based on our clinical trial results to date, we believe that using DEXTENZA for allergic conjunctivitis can create a low, tapered, consistent dose of dexamethasone, potentially minimizing or eliminating side effects associated with the eye drop formulation, while retaining the drug's anti-inflammatory effects.

We believe that allergic conjunctivitis represents a discrete potential market opportunity for preservative-free DEXTENZA because it is a physician-administered, hands-free, therapy administered in the office setting. We believe that many of the specialists who treat patients for post-surgical inflammation and pain also treat patients suffering from allergic conjunctivitis.

We commercially launched DEXTENZA for the treatment of ocular itching associated with allergic conjunctivitis in the first quarter of 2022 utilizing a small, dedicated and highly focused sales force of four key account managers and two field reimbursement managers that called exclusively on the offices of ophthalmologists and optometrists. In the fourth quarter of 2022, we redeployed this small sales force to join the DEXTENZA sales force focused on the ophthalmic surgery market, specifically cataract surgery, in ambulatory surgery centers, or ASCs, and hospital outpatient departments, or HOPDs. We believe that cataract surgeries represent a larger, near-term market opportunity and a faster return-on-investment.

Prevention of Wound Leaks Following Cataract Surgery

ReSure Sealant

ReSure Sealant is a topical liquid hydrogel that creates a temporary, adherent, soft and lubricious sealant to prevent post-surgical leakage from clear corneal incisions that are made during cataract surgery. The FDA granted marketing approval for ReSure Sealant in January 2014 and we commercially launched ReSure Sealant in the United States in February 2014.

We have received only limited revenues from ReSure Sealant to date as the product is only used in a minority of cataract surgeries and, currently, there is no direct separate reimbursement for the product—meaning ReSure Sealant is only reimbursed as part of a bundled payment for the associated surgery. As of the fourth quarter of 2021, we suspended the production of ReSure Sealant in order to focus our manufacturing resources on the commercialization of DEXTENZA. Currently, ReSure Sealant is not commercially available in the United States.

AffaMed License Agreement

In October 2020, we entered into a license agreement and collaboration with AffaMed Therapeutics Limited, or AffaMed, for the development and commercialization of DEXTENZA and OTX-TIC in mainland China, Taiwan, Hong Kong, Macau, South Korea, and the countries of the Association of Southeast Asian Nations. Under the terms of the agreement, we received an upfront payment of $12 million and became eligible to receive development, regulatory and commercial milestone payments and clinical development support payments of up to $91 million in the aggregate, as well as royalties from future product sales. In the fourth quarter of 2021, we received a $1 million milestone payment upon the approval by the FDA of an sNDA for DEXTENZA to include the treatment of ocular itching associated with allergic conjunctivitis as an additional indication; in the second quarter of 2022, we received a $2 million clinical support payment in connection with dosing the first subject in a Phase 2 clinical trial evaluating OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension. Royalties are tiered and will range from the low teens to low twenty percent range. In return, we agreed to grant AffaMed exclusive rights to develop and commercialize DEXTENZA for the treatment of post-surgical inflammation and pain following ophthalmic surgery and ocular itching in patients with allergic conjunctivitis, and OTX-TIC for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension in specified Asian markets. We retain the right to develop and commercialize DEXTENZA and OTX-TIC in all other global markets.

In January 2022, AffaMed announced that it had dosed its first patient in a real-world setting study conducted in China evaluating the safety and efficacy of DEXTENZA® (0.4mg dexamethasone ophthalmic insert) for the treatment of ocular inflammation and pain post-cataract surgery. This prospective, single-arm, real-world trial is designed to assess the safety and efficacy of DEXTENZA for the treatment of ocular inflammation and pain following cataract surgery in approximately 120 patients at the Bo'ao Super Hospital. The trial's primary efficacy endpoint is the absence of anterior

chamber cells in the study eye at Day 14, and the key secondary endpoint is the absence of pain in the study eye at Day 8.

In April 2022, AffaMed announced that DEXTENZA has been approved in Macau, China for the treatment of ocular inflammation and pain following ophthalmic surgery. We do not expect that DEXTENZA sales in Macau will result in material revenues to us.

Sales, Marketing and Distribution

We generally expect to retain commercial rights in the United States to any of our product candidates for which we may receive marketing approvals and which we believe we can successfully commercialize. In general, if we receive approval to market any of our product candidates in the United States, we plan to then evaluate the regulatory approval requirements and commercial potential for any such product candidate in Europe, Japan and other selected geographies. If we decide to commercialize our products outside of the United States, we expect to utilize a variety of types of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize any product of ours that receives marketing approval.

We sell DEXTENZA in the United States to a network of specialty distributors, who then resell DEXTENZA to ASCs and HOPDs. We have built a highly targeted, key account sales force of KAMs, or key account managers, Regional Directors, and FRMs or field reimbursement managers that focus on the ASCs and their affiliates responsible for the largest volumes of cataract surgery in the United States, with an initial emphasis on the approximately two million cataract procedures performed annually under Medicare Part B.

With the approval of DEXTENZA for the indication of ocular itching associated with allergic conjunctivitis, we launched a commercial effort in the first half of 2022 with four KAMs and two FRMs dedicated to selling DEXTENZA to the offices of ophthalmologists and optometrists, where the vast majority of prescriptions for allergies are written. As of the fourth quarter of 2022, we redeployed the office-focused personnel back to the ocular surgical market, calling on ASCs and HOPDs. In the third quarter of 2022, we implemented an off-invoice discount program whereby providers receive the discounted price immediately upon purchase, rather than having to wait until the end of the quarter for a rebate payment.

Manufacturing

We fabricate devices and drug products for use in our clinical trials, research and development and commercial efforts for all of our products and product candidates using current Good Manufacturing Practices, or cGMP, at our approximately 20,000 square foot facility located in Bedford, Massachusetts. In June 2016, we entered into a new lease agreement for approximately 71,000 square feet of a facility in Bedford, Massachusetts that primarily houses our research and development functions but may include additional manufacturing space in the future.

We purchase active pharmaceutical ingredient drug substance from independent suppliers on a purchase order basis for incorporation into our drug product candidates. We purchase our PEG and other raw materials from different vendors on a purchase order basis according to our specifications. While we believe that multiple vendors are available for each component we purchase, we have historically sole-sourced each component. We qualify vendors according to our quality system requirements. We do not have any long-term supply agreements in place for any raw materials or drug substances. We do not license any technology or pay any royalties to any of our drug or raw material vendors for the current or potential front and back-of-the-eye products.

We believe that our strategic investment in manufacturing capabilities allows us to advance product candidates at a more rapid pace and with more flexibility than a contract manufacturer, although we will continue to evaluate outsourcing unit operations for cost advantages. Our manufacturing capability also enables us to produce products in a cost-effective manner while retaining control over the manufacturing process and prioritizing the timing of internal programs.

Our manufacturing capabilities encompass the full manufacturing process through quality control and quality assurance and are integrated with our project teams from discovery through development and commercial release. This structure enables us to efficiently transfer research stage product concepts into manufacturing. We have designed our

manufacturing facility and processes to provide flexibility for the manufacture of different product candidates. We outsource sterilization services for our products.

We believe that we can scale our manufacturing processes to support DEXTENZA sales as well as development of our drug product candidates and the potential commercialization of such product candidates.

Intellectual Property

Our success depends in part on our ability to obtain and maintain proprietary protection for our products, 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 rely on patent protection, trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

We have issued patents and/or patent applications pending for all of our commercial products and product candidates, as well as trade secrets to protect proprietary manufacturing processes. As of March 1, 2023, patents and/or patent applications pending owned by us, are 95 pending applications: 5 pending provisional applications, 11 pending U.S. patent applications, 11 pending World Intellectual Property Organization applications and 68 foreign applications.

Certain of our U.S. patents and applications, and foreign counterparts, are Company owned and other U.S. patents and applications, and foreign counterparts have been in-licensed from Incept.

The following is a summary of patents and patent applications that cover our commercial products and potentially cover our product candidates:

OTX-TKI (axitinib intravitreal implant) for Wet AMD, DME and RVO

We own issued patents in the U.S. that cover this product candidate, with current expiration dates in 2041. Additional U.S. and foreign patent applications are pending.

OTX-TIC (travoprost intracameral implant) for open-angle glaucoma or ocular hypertension

We have licenses to pending U.S. applications and certain foreign patent applications pending that potentially cover this product candidate that, if granted, are expected to expire in 2037. We own pending patent applications in the U.S., and certain foreign counterparts, with the potential to cover this product candidate that, if granted, are expected to expire in 2041.

OTX-CSI (cyclosporine intracanalicular insert) for dry eye disease

We have licenses to U.S. patents, and certain foreign counterparts, that cover this product candidate, with current expiration dates in 2030. We own issued patents and pending patent applications in the U.S. that cover this product candidate with current expiration dates in 2037 and in 2041, and corresponding foreign patent applications that, if granted, are expected to expire in 2041.

OTX-DED (dexamethasone intracanalicular insert) for episodic dry eye disease

We have licenses to U.S. patents, and certain foreign counterparts, with current expiration dates in 2030. We own an issued patent that expires in 2037 that covers this product candidate and a pending patent application in the U.S., and certain foreign counterparts, with the potential to cover this product candidate that, if granted, are expected to expire in 2041.

DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg

We have licenses to U.S. patents, and certain foreign counterparts, with current expiration dates in 2030 that cover this product.

We also own a U.S. patent that covers this product with a current expiration date in 2037.

DEXTENZA (dexamethasone ophthalmic insert) 0.4 mg for allergic conjunctivitis

We have licenses to U.S. patents, and certain foreign counterparts, with current expiration dates in 2030 that cover this product. We also own a U.S. patent that covers this product with a current expiration date in 2037 and a pending patent application in the U.S., and certain foreign counterparts, with the potential to cover this product candidate that, if granted, is expected to expire in 2041.

ReSure Sealant

We have licenses to two U.S. patents that cover ReSure Sealant. One U.S. patent is expected to expire in 2024 and relating to the process of making and using hydrogel compositions, and one U.S. patent is expected to expire in 2032 and relates to certain features of the ReSure Sealant package.

The existence of patent applications does not guarantee that a patent will issue, or that any patent that does issue will cover the product or product candidate. Issued patents are subject to validity, enforceability and infringement challenges by third parties with uncertain chances of success.

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 United States Patent and Trademark Office in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over a commonly owned patent or a patent naming a common inventor and having an earlier expiration date. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration date of a U.S. patent for certain patents as partial compensation for the length of time the drug is under regulatory review while the patent is in force. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended.

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

We may rely, in some circumstances, on 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.

Licenses

Incept, LLC

In January 2012, we entered into an amended and restated license agreement, which we refer to as either the Prior Agreement or Original License, with Incept under which we hold an exclusive, worldwide, perpetual, irrevocable license under specified patents and technology owned or controlled by Incept to make, have made, use, offer for sale, sell, sublicense, have sublicensed, offer for sublicense and import, products delivered to or around the human eye for diagnostic, therapeutic or prophylactic purposes relating to all human ophthalmic diseases or conditions. This license covers a significant portion of the patent rights and the technology for DEXTENZA, ReSure Sealant and our hydrogel platform technology product candidates. The agreement supersedes an April 2007 license agreement between us and Incept. Amar Sawhney, our former President and Chief Executive Officer and former Executive Chairman of the Board of Directors, is a general partner of Incept.

On September 13, 2018, or the Effective Date, we entered into a second amended and restated license agreement, or the Second Amended Agreement, with Incept. The Second Amended Agreement amends and restates in full the Prior Agreement, to expand the scope of our intellectual property license and modify future intellectual property ownership and other rights thereunder.

License Rights; Ownership of Intellectual Property. We and Incept have agreed to expand the field of use of the exclusive, worldwide, perpetual, irrevocable license held by us under the Prior Agreement to include specified intellectual property rights and technology owned or controlled by Incept to make, have made, use, offer for sale, sell, sublicense, have sublicensed, offer for sublicense and import, (i) consistent with the Prior Agreement, products delivered to or around the human eye for diagnostic, therapeutic or prophylactic purposes relating to all human ophthalmic diseases or conditions, or the Ophthalmic Field of Use, and (ii) as a result of the expansion of the scope of the Original License, products delivered for the treatment of acute post-surgical pain or for the treatment of ear, nose and/or throat diseases or conditions, subject to specified exceptions, or the Additional Field of Use. We and Incept have further agreed to expand the field of use of the Original License for certain patents, patent applications and other rights pertaining to shape-changing hydrogel formulations thereunder, or the Shape-Changing IP, to include all fields except those involving the nerves and associated tissues specified in the Second Amended Agreement.

We will solely own, without a license to Incept, all intellectual property rights conceived solely by one or more individuals from our company, or the Company Individuals, after the Effective Date, subject to exceptions specified therein. Subject to certain exceptions specified in the Second Amended Agreement, Incept will own and license to the us (i) all intellectual property rights included in the Original License, or the Original IP, in the Ophthalmic Field of Use and the Additional Field of Use, (ii) intellectual property rights in the field of drug delivery conceived solely by the Company Individuals on or before the Effective Date, or Incept IP, and (iii) intellectual property rights in the field of drug delivery conceived by one or more Company Individuals jointly with one or more individuals from Incept, including Dr. Sawhney, or the Incept Individuals, after the Effective Date. These intellectual property rights are referred to as Joint IP, and, collectively with the Original IP and the Incept IP, as the Licensed IP.

Financial Terms. We and any of our sublicensees are obligated to pay Incept royalties as follows under the Second Amended Agreement: (i) consistent with the Prior Agreement, a royalty equal to a low single-digit percentage of net sales by the us or our affiliates of products, devices, materials, or components thereof, or Licensed Products, including or covered by Original IP, excluding the Shape-Changing IP, in the Ophthalmic Field of Use; (ii) a royalty equal to a mid-single-digit percentage of net sales by us or our affiliates of Licensed Products including or covered by Original IP, excluding the Shape-Changing IP, in the Additional Field of Use; and (iii) a royalty equal to a low single-digit percentage of net sales by us or our affiliates of Licensed Products including or covered by Incept IP or Joint IP in the field of drug delivery. Royalty obligations under the Second Amended Agreement commence with the first commercial sale of a Licensed Product described above and terminate upon the expiration of the last-to-expire patents included in the Licensed IP, as applicable. Any sublicensee of us also will be obligated to pay Incept royalties on net sales of Licensed Products made by it and will be bound by the terms of the Second Amended Agreement to the same extent as us. Additionally, at its sole discretion, Incept may require, as a condition of any sublicense by us in the Additional Field of Use and in exchange for a reduction in the royalties owed on net sales of Licensed Products described above, payments equal to a mid-teen percentage of any upfront payment and, subject to certain conditions, other payments received by us from the sublicensee.

Patent Prosecution and Litigation. Incept will continue to have sole control and responsibility for ongoing prosecution of patents included in the Original IP, and we will have sole control and responsibility for ongoing prosecution of patents and patent applications included in or arising under the Incept IP or Joint IP. The parties have agreed to work together in good faith to enter into a separate agreement under which, subject to certain limitations, we would assume control of the prosecution of patents and patent applications included in or arising under the Shape-Changing IP. We have the right, subject to certain conditions, to bring suit against third parties who infringe the patents included in the Original IP in the Ophthalmic Field of Use or the Additional Field of Use, patents included in the Incept IP in the drug delivery filed, patents included in the Joint IP in the drug delivery field, and patents included in the Shape-Changing IP in all fields except as described above. We have also agreed, if requested by Incept, to enter into a joint defense and prosecution agreement for the purpose of allowing the parties to share confidential and attorney-client privileged information regarding the possible infringement of one or more patents covered by the Second Amended Agreement. We are responsible for all costs incurred in prosecuting any infringement action it brings.

Term and Termination. The Second Amended Agreement will expire on the later of (i) the expiration or disclaimer by us of the last valid claim of an issued and unexpired patent included in the Licensed IP or (ii) the final unappealable rejection or abandonment of the last pending patent application arising under the Licensed IP. Either party may terminate the Second Amended Agreement in the event of the other party's insolvency, bankruptcy or comparable proceedings, or if the other party materially breaches the agreement and does not cure such breach during a specified cure period.

AffaMed License Agreement

On October 29, 2020, we entered into a license agreement, or the License Agreement, with AffaMed for the development and commercialization of DEXTENZA regarding ocular inflammation and pain following cataract surgery and allergic conjunctivitis, or collectively, the DEXTENZA Field, and for OTX-TIC, or collectively with DEXTENZA, the AffaMed Licensed Products, regarding open-angle glaucoma and ocular hypertension, or collectively, the TIC Field and, with the DEXTENZA Field, each a Field, in each case in mainland China, Taiwan, Hong Kong, Macau, South Korea, and the countries of the Association of Southeast Asian Nations, or collectively, the Territories. We retain development and commercialization rights for the AffaMed Licensed Products in the rest of the world.

Under the License Agreement, we granted AffaMed (i) a non-exclusive, royalty-free, non-sublicensable license under certain of our intellectual property rights and know-how to use the AffaMed Licensed Products in connection with specified activities in accordance with a development plan agreed between the parties and (ii) an exclusive, royalty-bearing, sublicensable, non-transferable (subject to specified exceptions), license under certain of our intellectual property rights and know-how to commercialize the AffaMed Licensed Products in the applicable Field in the Territories. We have further agreed not to, and to cause its affiliates or agents not to, develop or commercialize in the Territories (i) the AffaMed Licensed Products outside of the applicable Fields and (ii) any other product containing the same active pharmaceutical ingredients as the AffaMed Licensed Products and administered into the anterior chamber of the eye, in each case without AffaMed's prior written consent. AffaMed has agreed not to, and to cause its affiliates or agents not to, engage in the development, manufacture, or commercialization of any competing product in the Territories.

Under the terms of the License Agreement, we received upfront payments totaling $12 million in the fourth quarter of 2020. We also became eligible to receive up to an additional $91 million in aggregate, inclusive of a low-seven-figure clinical support payment, upon the achievement of certain development and commercial milestones. In the fourth quarter of 2021, we received a $1 million milestone payment under the License Agreement from AffaMed; in the second quarter of 2022, we received a $2 million clinical support payment in connection with dosing the first subject in a Phase 2 clinical trial evaluating OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension. There can be no guarantee, however, that any of the remaining milestones will be achieved. We are also entitled to receive tiered, escalating royalties on the net sales of the AffaMed Licensed Products ranging from a low-teen to low-twenties percentage. Royalties under the License Agreement are payable on an AffaMed Licensed Product-by-AffaMed Licensed Product and jurisdiction-by-jurisdiction basis and are subject to potential reductions in specified circumstances, subject to a specified floor.

Pursuant to the terms of the License Agreement, we are generally responsible for expenses related to the development of the AffaMed Licensed Products in the applicable Fields in the Territories, provided that AffaMed (i) reimburse us a low-teen percentage of expenses incurred in connection with certain clinical trials conducted by us and designed to support marketing approval of the AffaMed Licensed Product by FDA or the European Medicines Agency, or the Global Studies; (ii) is solely responsible for expenses incurred in connection with territory-specific clinical trials that it conducts in furtherance of the development plan agreed between the parties in the applicable Fields in the Territories, or the Local Studies; and (iii) reimburse us in full for expenses incurred in connection with obtaining and maintaining regulatory approvals of the AffaMed Licensed Products in the applicable Fields in the Territories. In the event AffaMed declines to participate in a Global Study or to conduct a Local Study in any jurisdiction in which we determine to conduct such a study, we are relieved of our obligation to provide AffaMed clinical data from such study, other than safety data, unless AffaMed subsequently reimburses us in the amounts described above plus a prespecified premium.

AffaMed is further obligated, at its sole cost and expense, to use commercially reasonable efforts to commercialize the AffaMed Licensed Products in the applicable Fields in the Territories. The License Agreement contemplates that the parties negotiate and enter into a future agreement requiring us to use commercially reasonable efforts to manufacture

and supply finished drug products in sufficient quantity for clinical development and commercialization of the AffaMed Licensed Products in the applicable Fields in the Territories.

In accordance with its terms, the License Agreement expires upon the expiration of the last royalty term for the last AffaMed Licensed Product in any applicable Field in the Territories. Either party may, subject to specified cure periods, terminate the License Agreement in the event of the other party's uncured breach. Either party may also terminate the License Agreement under specified circumstances relating to the other party's insolvency. During an established period following a change of control of us or our entry into a global licensing agreement that includes the Territories with a third party, we have the option to terminate the License Agreement, subject to a specified notice period and the repayment of any costs and expenses incurred by AffaMed in connection with the License Agreement, including upfront and milestone payments AffaMed has previously paid to us, at a prespecified premium. AffaMed has the right to terminate the License Agreement at any time following the completion of a Phase 3 clinical trial to evaluate OTX-TIC.

Mosaic Biosciences Agreement

In June 2021, we entered into an agreement with Mosaic to identify new targets and discover novel therapeutic agents aimed at the treatment of dry AMD. Our collaboration with Mosaic has yielded lead compounds that Mosaic has humanized and is now optimizing for our preclinical complement inhibitor program for the treatment of dry AMD. We own all intellectual property created under this agreement.

Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technologies, knowledge, experience and scientific resources provide us with competitive advantages, potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical and generic drug companies, and compounding pharmacies. 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. Many of our potential competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of each of our product candidates, if approved for marketing, are likely to be efficacy, safety, method of administration, convenience, price, the level of generic competition and the availability of coverage and adequate reimbursement from government and other third-party payors.

Because the active pharmaceutical ingredients in our product candidates are available on a generic basis, or are soon to be available on a generic basis, competitors will be able to offer and sell products with the same active pharmaceutical ingredient as our products so long as these competitors do not infringe the patents that we license. For example, our licensed patents related to our intracanalicular insert product candidates largely relate to the hydrogel composition of the intracanalicular inserts and certain drug-release features of the intracanalicular inserts. As such, if a third party were able to design around the formulation and process patents that we license and create a different formulation using a different production process not covered by our licensed patents or patent applications, we would likely be unable to prevent that third party from manufacturing and marketing its product.

Competitors of OTX-TKI

Our intravitreal implant for the treatment of wet AMD will compete with anti-VEGF compounds administered in their current formulation and prescribed for the treatment of wet AMD as these agents can in some instances deliver one to two months or more of therapeutic effect. They include Lucentis, Eylea, Beovu, Vabysmo and off-label use of the cancer therapy Avastin. Multiple companies, although all in early stages of development, are exploring ways to deliver anti-VEGF products in a sustained-release fashion, including Regeneron which is pursuing a high-dose version of Eyelea; Clearside Biomedical, Inc., which is pursuing a TKI (axitinib) administered into the suprachoroidal space;

Eyepoint Pharmaceuticals, Inc., which is pursuing a sustained-release bioerodible device containing a TKI (vorolanib) using its Durasert technology; Aerie Pharmaceuticals, which is pursuing development of a four to six month TKI implant (axitinib) using its Print® manufacturing technology; and Kodiak Sciences Inc., which is pursuing sustained release therapies based on its anti-VEGF biopolymer conjugate technology. In October 2021, Genentech received approval for Susvimo which utilizes the company's port delivery system for delivery of ranibizumab but has recently launched a voluntary recall of the product due to manufacturing issues. In addition, there are several companies pursuing gene therapy to treat retinal diseases including Adverum Biotechnologies, Inc. and REGENXBIO Inc. There also are a number of companies with products in development targeting the inhibition of the complement system to address retinal diseases, specifically geographic atrophy including Apellis Pharmaceuticals, IVERIC bio, Inc., Annexion Biosciences, Novartis (Gyroscope Therapeutics), Genentech/Ionis and Janssen Pharmaceuticals, among others. Apellis recently received approval of SYFOVRE as the first approved treatment for geographic atrophy.

Competitors of OTX-TIC

Allergan PLC, now owned by AbbVie, Inc., received approval in March 2020 of DURYSTA, a biodegradable bimatoprost intracameral implant consisting of a PGA and a biodegradable polymer matrix for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Allergan purchased ForSight VISION5 who was conducting a Phase 2 clinical trial with the Helios insert, a sustained-release ocular insert placed below the eyelid that delivers bimatoprost for the treatment of glaucoma. In February 2023, Glaukos, Inc. submitted an NDA for its iDose technology to deliver travoprost for the treatment of glaucoma. In addition, several other companies have announced their intention to develop products for treatment of glaucoma using sustained-release therapy, although each of these is at an early stage of development. Mati Therapeutics has conducted a Phase 2 clinical trial with an intracanalicular insert for the treatment of glaucoma.

Competitors of OTX-CSI and OTX-DED

A number of therapies are currently available for the treatment of dry eye disease in the United States. The most commonly used treatments for dry eye disease in the United States are over-the-counter eye drops, often referred to as "artificial tears," and there are three FDA-approved prescription eye drop therapies: Restasis, Xiidra and Cequa. Artificial tears are intended to supplement insufficient tear production or improve tear film instability but are primarily saline-based and provide only temporary relief. Restasis and Cequa, both calcineurin inhibitor immunosuppressants, and Xiidra, a LFA-1 antagonist, address chronic inflammation associated with dry eye disease. Kala Pharmaceuticals received approval in 2020 and launched EYSUVIS, (loteprednol etabonate ophthalmic suspension) 0.25% for the short term (up to two weeks) treatment of the signs and symptoms of dry eye disease. EYSUVIS was sold to Alcon in July 2022. Oyster Point Pharma received approval in 2021 for TYRVAYA (varenicline solution) Nasal Spray, a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease. Oyster Point was purchased by Viatris in November 2022. Other treatment options include ointments, gels, warm compresses, omega-3 fatty acid supplements and a number of medical devices. We are aware of many other companies developing therapies for dry eye disease, including Aerie Pharmaceuticals, Alcon, Aldeyra Therapeutics, Allergan, Aurinia Pharmaceuticals, Azura Ophthalmics, Bausch Health (Novaliq), HanAll BioPharma, Johnson & Johnson, Mitotech, Novartis, Parion Sciences, ReGenTree, Silk Technologies, Sylentis, TearSolutions, and TopiVert Pharma.

Competitors of DEXTENZA

Icon Biosciences, Inc. received FDA approval of DEXYCU in February 2018. DEXYCU is an injection of dexamethasone at the time of surgery into the posterior chamber of the eye (behind the iris) to treat inflammation associated with cataract surgery. Icon Biosciences Inc. was subsequently bought by pSvidia Corporation in March 2018 and, at the same time, the new entity was renamed Eyepoint. Eyepoint launched DEXYCU commercially in the first quarter of 2019. OMIDRIA, purchased by Rayner Surgical Group Limited, is a prescription medication used during cataract surgery. According to the OMIDRIA website, this product helps the black part in the center of your eye (pupil) stay open (dilated) during cataract surgery and decreases eye pain after surgery.

Competitors of ReSure Sealant

ReSure Sealant is the first and only surgical sealant approved for ophthalmic use in the United States. Outside the United States, Beaver Visitec is commercializing its product OcuSeal, which is designed to provide a protective hydrogel film barrier to stabilize ocular wounds. This product has received a CE Mark in Europe but is not approved for

use in the United States. Sutures are the primary alternative device for closing ophthalmic wounds. Most commonly, however, a technique called stromal hydration, which involves the localized injection of a balanced salt solution at the wound edges, is often used to facilitate the sealing of a wound.

Government Regulation

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, quality control, clearance, approval, pricing, sales, reimbursement, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products and medical devices. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, 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 FDCA and related regulations. Drugs are also subject to other federal, state and local statutes and regulations. Biological products are licensed for marketing under the Public Health Service Act, or PHSA, and subject to regulation under the FDCA and related regulations, and other federal, state and local statutes and regulations. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products is referred to as a sponsor. A sponsor seeking approval to market and distribute a new drug or biological 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;
- design of a clinical 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 site before each clinical trial may be initiated;
- 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;
- preparation and submission to the FDA of a new drug application, or NDA, for a drug candidate product and a biological licensing application, or BLA, for a biological product requesting marketing for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with current Good Manufacturing Practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of clinical data;
- payment of user fees and securing FDA approval of the NDA or BLA; 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

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated product, as well as *in vitro* and animal studies to assess the safety and activity of the investigational product for initial testing in humans and to establish a rationale for therapeutic use. These studies are generally referred to as IND-enabling studies. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations and standards and the United States Department of Agriculture's Animal Welfare Act. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND.

Companies usually must complete some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and must also develop additional information about the chemistry and physical characteristics of the investigational product and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the candidate product and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the candidate product does not undergo unacceptable deterioration over its shelf life.

The IND and IRB Processes

Clinical trials involve the administration of the 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 voluntary 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. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biologic that is not the subject of an approved NDA or BLA. 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. 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. For our intracanalicular insert product candidates, we have typically conducted our initial and earlier-stage clinical trials outside the United States. We generally plan to conduct our later stage and pivotal clinical trials of our intracanalicular insert product candidates in the United States.

A sponsor may choose, but is not required, to conduct a foreign clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain regulatory requirements of the FDA in order to use the trial as support for an IND or application for marketing approval. Specifically, the FDA requires such trials to be conducted in accordance with GCP, including review and approval by an independent ethics committee and informed consent from subjects. The GCP requirements encompass both ethical and data integrity standards for clinical trials. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical trials, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign trials are conducted in a manner comparable to that required for IND trials.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove 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.

The FDA's primary objectives in reviewing an IND are to assure the safety and rights of patients and to help assure that the quality of the investigation will be adequate to permit an evaluation of the drug's effectiveness and safety and of the biological product's safety, purity and potency. The decision to terminate development of an investigational drug or biological product may be made by either a health authority body such as the FDA, an IRB or ethics committee, or by us for various reasons. 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 DSMB, or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Reporting Clinical Trial Results

Under the PHSA, sponsors of clinical trials of certain FDA-regulated products, including prescription drugs and biologics, 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. Although sponsors are also obligated to disclose the results of their clinical trials after completion, disclosure of the results can be delayed in some cases for up to two years after the date of completion of the trial. The NIH's Final Rule on registration and reporting requirements for clinical trials became effective in 2017. Although the FDA has historically not enforced these reporting requirements due to the Department of Health and Human Services (HHS) long delay in issuing final implementing regulations, 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. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

There is no obligation for a sponsor to make its investigational products available for expanded access; however, as required by amendments to the FDCA included in the 21st Century Cures Act, or the Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests with respect to product candidates in development to treat serious diseases or conditions, it must make that policy publicly available. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study for a covered investigational product; or 15 days after the investigational product receives designation from the FDA as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Studies in Support of an NDA or BLA

Clinical trials involve the administration of the 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 three sequential phases, which may overlap or be combined:

- Phase 1: The drug or biologic is initially introduced into a small number of healthy human subjects or 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 drug or biologic 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 3: The drug or biologic 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, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

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, as noted above, 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 began requiring 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.

In some cases, the FDA may approve an NDA or BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials, typically referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials, such as to verify clinical

benefit in the case of products approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting mandatory Phase 4 clinical trials could result in withdrawal of FDA approval for products.

In response to the COVID-19 pandemic, FDA issued guidance on March 18, 2020, and has updated it periodically since that time to address the conduct of clinical trials during the pandemic. The guidance sets out a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study as a result of COVID-19; a list of all study participants affected by COVID-19-related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study, among other things. On January 30, 2023, the Biden Administration announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidance's, including the clinical trial guidance and updates thereto. At this point, it is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates.

Interactions with FDA During the Clinical Development Program

Following the clearance of an IND and the commencement of clinical trials, the sponsor will continue to have interactions with the FDA. Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product candidate; and any clinically important increase in the occurrence of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

In addition, sponsors are given opportunities to meet with the FDA at certain points in the clinical development program. Specifically, sponsors may meet with the FDA prior to the submission of an IND (pre-IND meeting), at the end of Phase 2 clinical trial (EOP2 meeting) and before an NDA or BLA is submitted (pre-NDA or pre-BLA meeting). Meetings at other times may also be requested. There are four types of meetings that occur between sponsors and the FDA. Type A meetings are those that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Type B meetings include pre-IND and pre-NDA/pre-BLA meetings, as well as end of phase meetings such as EOP2 meetings. A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product, including for example meetings to facilitate early consultations on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. Finally, a Type D meeting is focused on a narrow set of issues, which should be limited to no more than two focused topics, and should not require input from more than three disciplines or Divisions.

These meetings provide an opportunity for the sponsor to share information about the data gathered to date with the FDA and for the FDA to provide advice on the next phase of development. For example, at an EOP2 meeting, a sponsor may discuss its Phase 2 clinical results and present its plans for the pivotal Phase 3 clinical trial(s) that it believes will support the approval of the new product. Such meetings may be conducted in person, via teleconference/videoconference or written response only with minutes reflecting the questions that the sponsor posed to the FDA and the FDA's responses. The FDA has indicated that its responses, as conveyed in meeting minutes and advice letters, only constitute mere recommendations and/or advice made to a sponsor and, as such, sponsors are not bound by such recommendations and/or advice. Nonetheless, from a practical perspective, a sponsor's failure to follow the FDA's recommendations for design of a clinical program may put the program at significant risk of failure.

Manufacturing and Other Regulatory Requirements

Concurrently 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.

The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug or biologic undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States.

Pediatric Studies

Under the Pediatric Research Equity Act, or PREA, applications and certain types of supplements to applications 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. The sponsor must submit an initial Pediatric Study Plan, or PSP, within 60 days of an EOP2 meeting or as may be agreed between the sponsor and the FDA. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The sponsor and the FDA must reach agreement on a final plan. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. Pursuant to the Food and Drug Administration Safety and Innovation Act of 2012, or FDASIA, the FDA must send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. It further requires the FDA to publicly post the PREA Non-Compliance letter and sponsor's response. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although the FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease. The FDA also maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, 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."

Section 505(b)(2) thus authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the sponsor. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) sponsor can establish that reliance on the FDA's previous approval is scientifically appropriate, the sponsor may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) sponsor.

If we obtain favorable results in our clinical trials, we plan to submit NDAs for our product candidates under Section 505(b)(2).

Acceptance and Review of NDAs and BLAs

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, along with information relating to the product's chemistry, manufacturing, controls, safety updates, patent information, abuse information and proposed labeling, are submitted to the FDA as part of an application requesting approval to market the product candidate for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of a drug product and the safety, potency and purity of the biological product to the satisfaction of the FDA. The fee required for the submission and review of an application under the Prescription Drug User Fee Act, or PDUFA, is substantial (for example, for FY2023 this application fee is approximately $3.25 million), and the sponsor of an approved application is also subject to an annual program fee, currently more than $394,000 per eligible prescription product. These fees are typically adjusted annually, and exemptions and waivers may be available under certain circumstances, such as where a waiver is necessary to protect the public health, where the fee would present a significant barrier to innovation, or where the sponsor is a small business submitting its first human therapeutic application for review.

The FDA conducts a preliminary review of all applications within 60 days of receipt and must inform the sponsor at that time or before whether an application is sufficiently complete to permit substantive review. In pertinent part, FDA's regulations state that an application "shall not be considered as filed until all pertinent information and data have been received" by the FDA. 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. Typically, an RTF will be based on administrative incompleteness, such as clear omission of information or sections of required information; scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety and efficacy or provide adequate directions for use; or inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

After the submission is accepted for filing, the FDA begins an in-depth substantive review of the application. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective for its intended use, whether it has an acceptable purity profile and whether the product is being manufactured in accordance with cGMP. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard application that is a new molecular entity, and six months from

the filing date for an application with "priority review." The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission. Despite these review goals, it is not uncommon for FDA review of an application to extend beyond the PDUFA target action date.

In connection with its review of an application, the FDA will typically submit information requests to the sponsor and set deadlines for responses thereto. The FDA will also conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether the manufacturing processes and facilities comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and are adequate to assure consistent production of the product within required specifications.

The FDA also may inspect the sponsor and one or more clinical trial sites to assure compliance with IND and GCP requirements and the integrity of the clinical data submitted to the FDA. With passage of FDORA, Congress clarified 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 FDA as well as other persons holding study records or involved in the study process. To ensure cGMP and GCP compliance by its employees and third-party contractors, a sponsor may incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

Additionally, the FDA may refer an application, including applications for novel product candidates which present difficult questions of safety or efficacy, to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. 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 recommendation of an advisory committee, but it considers such recommendations when making final decisions on approval. Data from clinical trials are not always conclusive, and the FDA or its advisory committee may interpret data differently than the sponsor interprets the same data. The FDA may also re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the sponsor during the review process.

The FDA also may require submission of a Risk Evaluation and Mitigation Strategy, or REMS, if it determines that a REMS is necessary to ensure that the benefits of the product outweigh its risks and to assure the safe use of the product. The REMS could include medication guides, physician communication plans, assessment plans and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. The FDA determines the requirement for a REMS, as well as the specific REMS provisions, on a case-by-case basis. If the FDA concludes a REMS is needed, the sponsor of the application must submit a proposed REMS and the FDA will not approve the application without a REMS.

Decisions on NDAs and BLAs

The FDA reviews a sponsor 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 term "substantial evidence" is defined under the FDCA as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the product involved, on the basis of which it could fairly and responsibly be concluded by such experts that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

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, FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard. This approach was subsequently endorsed by Congress in 1998 with legislation providing, in pertinent part, that "If FDA determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, FDA may consider such data and evidence to constitute substantial evidence." This modification to the law recognized the potential for FDA to find that one adequate and well controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness. In December 2019, FDA issued draft guidance further

explaining the studies that are needed to establish substantial evidence of effectiveness. It has not yet finalized that guidance.

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 CRL or an approval letter. To reach this determination, the FDA must determine that the drug is effective and that its expected benefits 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 BLA. This assessment is also informed by other factors, including: the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks. In connection with this assessment, the FDA review team will assemble all individual reviews and other documents into an "action package," which becomes the record for FDA review. The review team then issues a recommendation, and a senior FDA official makes a decision.

A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. 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. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time- consuming requirements related to clinical trials, preclinical studies or manufacturing. 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. The FDA has committed to reviewing resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with the submission of this additional information, however, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. The FDA has taken the position that a CRL is not final agency action making the determination subject to judicial review. For those seeking to challenge FDA's CRL decision, the FDA has indicated that sponsors may request a formal hearing on the CRL or file a request for reconsideration or a request for a formal dispute resolution.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications. That is, the approval will be limited to the conditions of use (e.g., patient population, indication) described in the FDA-approved labeling. Further, depending on the specific risk(s) to be addressed, the FDA may require that contraindications, warnings or precautions be included in the product labeling, require that post-approval trials, including Phase 4 clinical trials, be conducted to further assess a product's safety after approval, require testing and surveillance programs to monitor the product after commercialization or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a 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-marketing trials or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Under the Ensuring Innovation Act, which was signed into law in April 2021, the FDA must publish action packages summarizing its decisions to approve new drugs and biologics within 30 days of approval of such products. To date, CRLs are not publicly available documents.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug 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, or IMM, 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. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

With passage of FDORA, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to: require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded, require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to FDA every six months until the study is completed; and use expedited procedures to withdraw accelerated approval of an NDA or BLA after the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the FDA to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.

Post-Approval Regulation

Drugs and biologics manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

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. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. 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, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, 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 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:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- 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. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the HHS, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic.

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, or PIE Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products and product candidates 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 and product candidates in development to payors, including unapproved uses of approved products.

In addition, the distribution of prescription pharmaceutical products is subject to a variety of federal and state laws, the most recent of which is still in the process of being phased into the U.S. supply chain and regulatory framework. The Prescription Drug Marketing Act, or PDMA, was the first federal law to set minimum standards for the registration and regulation of drug distributors by the states and to regulate the distribution of drug samples. Today, both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. Congress more recently enacted the Drug Supply Chain Security Act, or DSCSA, which made significant amendments to the FDCA, including by replacing certain provisions from the PDMA pertaining to wholesale distribution of prescription drugs with a more comprehensive statutory scheme. The DSCSA now requires uniform national standards for wholesale distribution and, for the first time, for third-party logistics providers; it also provides for preemption of certain state laws in the areas of licensure and prescription drug traceability.

Generic Drugs and Regulatory Exclusivity

In 1984, with passage of the Hatch-Waxman Act, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs and it also enacted Section 505(b)(2). To obtain approval of a generic drug, a sponsor must submit an abbreviated new drug application, or ANDA, to the agency.

In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD.

Under the Hatch-Waxman Act, the FDA may not approve an ANDA or 505(b)(2) application until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity, or NCE. For the purposes of this provision, FDA has consistently taken the position that an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. This interpretation was confirmed with enactment of the Ensuring Innovation Act in April 2021. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, a generic or follow-on drug application may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the sponsor may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the sponsor and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as new indications, dosage forms, route of administration or combination of ingredients. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs or 505(b)(2) NDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product; rather, 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 follow-on applications for drugs containing the original active ingredient.

Five-year and three-year exclusivity also will not delay the submission or approval of a traditional NDA filed under Section 505(b)(1) of the FDCA; however, a sponsor submitting a traditional 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.

As part of the submission of an NDA or certain supplemental applications, NDA sponsors are required to list with the FDA each patent with claims that cover the sponsor's product or an approved method of using the product. Upon approval of a new drug, each of the patents listed in the application for the drug is then published in the Orange Book. The FDA's regulations governing patient listings were largely codified into law with enactment of the Orange Book Modernization Act in January 2021. When an ANDA sponsor files its application with the FDA, the sponsor is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book. Specifically, the ANDA sponsor must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. Moreover, to the extent that the Section 505(b)(2) NDA sponsor is relying on studies conducted for an already approved product, the sponsor also is required to certify to the FDA concerning any patents listed for the NDA-approved product in the Orange Book to the same extent that an ANDA sponsor would.

If the generic drug or follow-on drug sponsor does not challenge the innovator's listed patents, FDA will not approve the ANDA or 505(b)(2) application until all the listed patents claiming the referenced product have expired. A certification that the new generic product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the ANDA sponsor has provided a Paragraph IV certification to the FDA, the sponsor must also send notice of the Paragraph IV certification to the NDA owner and patent holders once the ANDA has been accepted for filing by the FDA. The NDA owner and patent holders

may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earliest of 30 months after the receipt of the Paragraph IV notice, expiration of the patent and a decision in the infringement case that is favorable to the ANDA or 505(b)(2) NDA sponsor.

Regulatory Exclusivity Governing Biologics

When a biological product is licensed for marketing by FDA with approval of a BLA, the product may be entitled to certain types of market and data exclusivity barring FDA from approving competing products for certain periods of time. In March 2010, the Patient Protection and Affordable Care Act was enacted in the United States and included the Biologics Price Competition and Innovation Act of 2009, or the BPCIA. The BPCIA amended the PHSA to create an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological 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 to reviewing and licensing biosimilars and interchangeable biosimilars under the PHSA, including a draft guidance issued in November 2020 that seeks to provide additional clarity to manufacturers of interchangeable biosimilars.

Under the BPCIA, a manufacturer may submit an application for a product that is "biosimilar to" a previously approved biological product, which the statute refers to as 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 the proposed biosimilar product in terms of safety, purity and potency. The biosimilar sponsor may demonstrate that its product is biosimilar to the reference product on the basis of data from analytical studies, animal studies and one or more clinical studies to demonstrate safety, purity and potency in one or more appropriate conditions of use for which the reference product is approved. In addition, the sponsor must show that the biosimilar and reference products have the same mechanism of action for the conditions of use on the label, route of administration, dosage and strength, and the production facility must meet standards designed to assure product safety, purity and potency.

For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find not only that the product is biosimilar to the reference product but also that it can be expected to produce the same clinical results as the reference product such that the two products may be switched without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. Upon licensure by the FDA, an interchangeable biosimilar may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. Following approval of the interchangeable biosimilar product, the FDA may not grant interchangeability status for any second biosimilar until one year after the first commercial marketing of the first interchangeable biosimilar product. In December 2022, Congress clarified through FDORA that FDA may approve multiple first interchangeable biosimilar biological products so long as the products are all approved on the first day on which such a product is approved as interchangeable with the reference product.

A reference biological product is granted 12 years of exclusivity from the time of first licensure of the product, and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product. Even if a product is considered to be a reference product eligible for exclusivity, however, 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. 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, since passage of the BPCIA, many states have passed laws or amendments to laws, which address pharmacy practices involving biosimilar products.

Pediatric Exclusivity

Pediatric exclusivity is a type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of exclusivity. For drug products, the six-month exclusivity may be attached to the term of any existing patent or regulatory exclusivity, including the orphan exclusivity and regulatory exclusivities available under the Hatch-Waxman Act. For biologic products, the six month period may be attached to any existing

regulatory exclusivities but not to any patent terms. The conditions for pediatric exclusivity include the FDA's determination that information relating to the use of a new product in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric clinical trials, and the sponsor agreeing to perform, and reporting on, the requested clinical trials within the statutory timeframe. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patents that cover the product are extended by six months. Although this is not a patent term extension, it effectively extends the regulatory period during which the FDA cannot approve another application. 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 patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by the proposed product.

Patent Term Restoration and Extension

In the United States, a patent claiming a new product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch Waxman Act, which permits a patent extension of up to five years for patent term lost during product development and FDA regulatory review. Assuming grant of the patent for which the extension is sought, the restoration period for a patent covering a product is typically one half the time between the effective date of the IND involving human beings and the submission date of the NDA or BLA, plus the time between the submission date of the application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension in consultation with the FDA.

Review and Approval of Medical Devices in the United States

Medical devices in the United States are strictly regulated by the FDA. Under the FDCA, a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is, among other things: intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes. This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. If not, it is generally a medical device.

Unless an exemption applies, a new medical device may not be marketed in the United States unless and until it has been cleared through filing of a 510(k) premarket notification, or 510(k), or approved by the FDA pursuant to a PMA application. The information that must be submitted to the FDA in order to obtain clearance or approval to market a new medical device varies depending on how the medical device is classified by the FDA. Medical devices are classified into one of three classes on the basis of the controls deemed by the FDA to be necessary to reasonably ensure their safety and effectiveness.

Class I devices are low-risk devices for which reasonable assurance of safety and effectiveness can be provided by adherence to the FDA's general controls for medical devices, which include applicable portions of the FDA's Quality System Regulation, or QSR, facility registration and product listing, reporting of adverse medical events and malfunctions and appropriate, truthful and non-misleading labeling, advertising and promotional materials. Many Class I devices are exempt from premarket regulation; however, some Class I devices require premarket clearance by the FDA through the 510(k) premarket notification process.

Class II devices are moderate-risk devices and are subject to the FDA's general controls, and any other special controls, such as performance standards, post-market surveillance, and FDA guidelines, deemed necessary by the FDA

to provide reasonable assurance of the devices' safety and effectiveness. Premarket review and clearance by the FDA for Class II devices are accomplished through the 510(k) premarket notification procedure, although some Class II devices are exempt from the 510(k) requirements. Premarket notifications are subject to user fees, unless a specific exemption applies.

Class III devices are deemed by the FDA to pose the greatest risk, such as those for which reasonable assurance of the device's safety and effectiveness cannot be assured solely by the general controls and special controls described above and that are life-sustaining or life-supporting. A PMA application must provide valid scientific evidence, typically extensive preclinical and clinical trial data and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications (and supplemental PMA applications) are subject to significantly higher user fees than are 510(k) premarket notifications.

510(k) Premarket Notification

To obtain 510(k) clearance, a manufacturer must submit a premarket notification demonstrating that the proposed device is "substantially equivalent" to a predicate device, which is a previously cleared 510(k) device or a pre-amendment device that was in commercial distribution before May 28, 1976, for which the FDA has not yet called for the submission of a PMA application. The FDA's 510(k) clearance pathway usually takes from three to 12 months from the date the application is submitted and filed with the FDA, but it can take significantly longer and clearance is never assured. The FDA has issued guidance documents meant to expedite review of a 510(k) and facilitate interactions between the sponsor and the FDA. To demonstrate substantial equivalence, a manufacturer must show that the device has the same intended use as a predicate device and the same technological characteristics, or the same intended use and different technological characteristics and does not raise new questions of safety and effectiveness than the predicate device.

Most 510(k)s do not require clinical data for clearance, but the FDA may request such data.

The FDA seeks to review and act on a 510(k) within 90 days of submission, but it may take longer if the agency finds that it requires more information to review the 510(k). If the FDA determines that the device is substantially equivalent to a predicate device, the subject device may be marketed. However, if the FDA concludes that a new device is not substantially equivalent to a predicate device, the new device will be classified in Class III and the manufacturer will be required to submit a PMA application to market the product. Devices of a new type that the FDA has not previously classified based on risk are automatically classified into Class III by operation of section 513(f)(1) of the FDCA, regardless of the level of risk they pose. To avoid requiring PMA review of low- to moderate-risk devices classified in Class III by operation of law, Congress enacted section 513(f)(2) of the FDCA. This provision allows the FDA to classify a low- to moderate-risk device not previously classified into Class I or II, a process known as the *de novo* process. A company may apply directly to the FDA for classification of its device as *de novo* or may submit a de novo petition within 30 days of receiving a not substantially equivalent determination.

Modifications to a 510(k)-cleared medical device may require the submission of another 510(k). Modifications to a 510(k)-cleared device frequently require the submission of a traditional 510(k), but modifications meeting certain conditions may be candidates for FDA review under a Special 510(k). If a device modification requires the submission of a 510(k), but the modification does not affect the intended use of the device or alter the fundamental technology of the device, then summary information that results from the design control process associated with the cleared device can serve as the basis for clearing the application. A Special 510(k) allows a manufacturer to declare conformance to design controls without providing new data. When the modification involves a change in material, the nature of the "new" material will determine whether a traditional or Special 510(k) is necessary.

Any modification to a 510(k)-cleared product that would constitute a major change in its intended use or any change that could significantly affect the safety or effectiveness of the device may, in some circumstances, requires the submission of a PMA application, if the change raises complex or novel scientific issues or the product has a new intended use. A manufacturer may be required to submit extensive pre-clinical and clinical data depending on the nature of the changes.

The FDA requires every manufacturer to make the determination regarding the need for a new 510(k) submission in the first instance, but the FDA may review any manufacturer's decision. If the FDA disagrees with the manufacturer's determination and requires new 510(k) clearances or PMA application approvals for modifications to previously cleared

products for which the manufacturer concluded that new clearances or approvals are unnecessary, the manufacturer may be required to cease marketing or distribution of the products or to recall the modified product until it obtains clearance or approval, and the manufacturer may be subject to significant regulatory fines or penalties. In addition, the FDA is currently evaluating the 510(k) process and may make substantial changes to industry requirements.

Premarket Approval Application

The PMA application process for approval to market a medical device is more complex, costly, and time-consuming than the 510(k) clearance procedure. A PMA application must be supported by extensive data, including technical information regarding device design and development, preclinical studies, clinical trials, manufacturing and controls information and labeling information that demonstrate the safety and effectiveness of the device for its intended use. After a PMA application is submitted, the FDA has 45 days to determine whether it is sufficiently complete to permit a substantive review. If the PMA application is complete, the FDA will file the PMA application. If the FDA accepts the application for filing, the agency will begin an in-depth substantive review of the application. By statute, the FDA has 180 days to review the application although, generally, review of the application often takes between one and three years, and may take significantly longer. If the FDA has questions, it will likely issue a first major deficiency letter within 150 days of filing. It may also refer the PMA application to an FDA advisory panel for additional review, and will conduct a preapproval inspection of the manufacturing facility to ensure compliance with the QSR, either of which could extend the 180-day response target. In addition, the FDA may request additional information or request the performance of additional clinical trials in which case the PMA application approval may be delayed while the trials are conducted and the data acquired are submitted in an amendment to the PMA. Even with additional trials, the FDA may not approve the PMA application.

If the FDA's evaluations of both the PMA application and the manufacturing facilities are favorable, the FDA will either issue an approval letter authorizing commercial marketing or an approvable letter that usually contains a number of conditions that must be met in order to secure final approval. If the FDA's evaluations are not favorable, the FDA will deny approval of the PMA application or issue a not approvable letter. The PMA application process, including the gathering of clinical and nonclinical data and the submission to and review by the FDA, can take several years, and the process can be expensive and uncertain. Moreover, even if the FDA approves a PMA application, the FDA may approve the device with an indication that is narrower or more limited than originally sought. The FDA can impose post-approval conditions that it believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. After approval of a PMA application, a new PMA application or PMA application supplement may be required for a modification to the device, its labeling, or its manufacturing process. PMA application supplements often require submission of the same type of information as an initial PMA application, except that the supplement is limited to information needed to support any changes from the device covered by the approved PMA application and may or may not require as extensive technical or clinical data or the convening of an advisory panel. The time for review of a PMA application supplement may vary depending on the type of change, but it can be lengthy. In addition, in some cases the FDA might require additional clinical data.

PMA applications are subject to an application fee. For federal fiscal year 2023, the standard fee is $441,547 and the small business fee is $110,387.

Investigational Device Exemption

A clinical trial is typically required for a PMA application and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and non-significant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices are devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. A non-significant risk device study requires only IRB approval prior to initiation of a clinical study.

An IDE application must be supported by appropriate data, such as animal and laboratory testing results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. An IDE application is

considered approved 30 days after it has been received by the FDA, unless the FDA otherwise informs the sponsor prior to 30 calendar days from the date of receipt, that the IDE is approved, approved with conditions, or disapproved. The FDA typically grants IDE approval for a specified number of subjects to be enrolled at specified study centers. The clinical trial must be conducted in accordance with applicable regulations, including but not limited to the FDA's IDE regulations and GCP. The investigators must obtain subject informed consent, rigorously follow the investigational plan and study protocol, control the disposition of investigational devices, and comply with all reporting and record keeping requirements. A clinical trial may be suspended or terminated by the FDA, the IRB or the sponsor at any time for various reasons, including a belief that the risks to the study participants outweigh the benefits of participation in the trial. Approval of an IDE does not bind the FDA to accept the results of the trial as sufficient to prove the product's safety and efficacy, even if the trial meets its intended success criteria.

Post-Marketing Restrictions and Enforcement

After a device is placed on the market, numerous regulatory requirements apply. These include but are not limited to:

- submitting and updating establishment registration and device listings with the FDA;
- compliance with the QSR, which require manufacturers to follow stringent design, testing, control, documentation, record maintenance, including maintenance of complaint and related investigation files, and other quality assurance controls during the manufacturing process;
- unannounced routine or for-cause device inspections by the FDA, which may include our suppliers' facilities labeling regulations, which prohibit the promotion of products for uncleared or unapproved or "off-label" uses and impose other restrictions on labeling; and
- post-approval restrictions or conditions, including requirements to conduct post-market surveillance studies to establish continued safety data or tracking products through the chain of distribution to the patient level.

Under the FDA medical device reporting, or MDR, regulations, medical device manufacturers are required to report to the FDA information that a device has or may have caused or contributed to a death or serious injury or has malfunctioned in a way that would likely cause or contribute to death or serious injury if the malfunction of the device or a similar device of such manufacturer were to recur. The decision to file an MDR involves a judgment by the manufacturer. If the FDA disagrees with the manufacturer's determination, the FDA can take enforcement action.

Additionally, the FDA has the authority to require the recall of commercialized products in the event of material deficiencies or defects in design or manufacture. The authority to require a recall must be based on an FDA finding that there is reasonable probability that the device would cause serious injury or death. Manufacturers may, under their own initiative, recall a product if any material deficiency in a device is found. The FDA requires that certain classifications of recalls be reported to the FDA within 10 working days after the recall is initiated.

The failure to comply with applicable regulatory requirements can result in enforcement action by the FDA, which may include any of the following sanctions:

- untitled letters, warning letters, fines, injunctions or civil penalties;
- recalls, detentions or seizures of products;
- operating restrictions;
- delays in the introduction of products into the market;
- total or partial suspension of production;

- delay or refusal of the FDA or other regulators to grant 510(k) clearance or PMA application approvals of new products;

- withdrawals of 510(k) clearance or PMA application approvals; or

- in the most serious cases, criminal prosecution.

To ensure compliance with regulatory requirements, medical device manufacturers are subject to market surveillance and periodic, pre-scheduled and unannounced inspections by the FDA, and these inspections may include the manufacturing facilities of subcontractors.

Review and Approval of Combination Products in the United States

- A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under FDA's regulations, a combination product is defined to include: a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity (a "single-entity" combination product);

- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products ("co-packaged" combination product);

- a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product (a "cross-labeled" combination product); or

- any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (a "cross-labeled" investigational combination product).

The FDA has established an Office of Combination Products to serve as a focal point for combination product issues and for medical product classification and assignment issues for agency staff and industry. That office issues guidance and regulations to clarify the regulation of combination products, and is responsible for assigning products to an FDA center for premarket review and regulation where their classification or assignment is unclear or in dispute. Combination products are assigned to an FDA center based on a determination of the "primary mode of action" or PMOA of the combination product. The FDCA defines PMOA as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." For example, if the PMOA of a device-biological combination product is attributable to the biological product, the FDA Division responsible for premarket review of that biological product would have primary jurisdiction for the combination product. One investigational application is generally sufficient for a combination product, but that application must include all information on the entire combination product. In most cases, the type of investigational application is that typically required by the lead center. Thus, if the drug constituent part of a drug/device combination product provides the PMOA, the investigation would be under an IND.

Federal and State Data Privacy Laws

There are multiple privacy and data security laws that may impact our business activities, in the United States and in other countries where we conduct trials or where we may do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the health care industry generally, under the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, the HHS has issued regulations to protect the privacy and security of protected health information, or PHI, used or disclosed by covered entities including certain healthcare providers, health plans and healthcare clearinghouses. HIPAA also regulates standardization of data content, codes and formats used in healthcare transactions and standardization of identifiers for health plans and providers. HIPAA also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. HIPAA may apply to us in certain

circumstances and may also apply to our business partners in ways that may impact our relationships with them. Our clinical trials are regulated by the Common Rule, which also includes specific privacy-related provisions. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that may be applicable to our business. In addition to possible federal civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. State attorneys general also have authority to enforce state privacy and security laws. New laws and regulations governing privacy and security may be adopted in the future as well.

At the state level, California has enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020 and requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023, and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah, and Connecticut, already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our current or future business activities, including certain clinical research, sales and marketing practices and the provision of certain items and services to our customers, could be subject to challenge under one or more of such privacy and data security laws. The heightening compliance environment and the need to build and maintain robust and secure systems to comply with different privacy compliance and/or reporting requirements in multiple jurisdictions could increase the possibility that a healthcare company may fail to comply fully with one or more of these requirements. If our operations are found to be in violation of any of the privacy or data security laws or regulations described above that are applicable to us, or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal, civil and administrative penalties, damages, fines, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a consent decree or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any product candidates we may develop, once approved, are sold in a foreign country, we may be subject to similar foreign laws.

Review and Approval of Medical Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Clinical Trial Approval

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 clinical 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 European Union at the EudraCT website: https://eudract.ema.europa.eu.

Marketing Authorization

To obtain marketing approval of a drug under European Union regulatory systems, a sponsor must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the European Medicines Agency, or EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to sponsors who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the sponsor, known as the reference member state. Under this procedure, a sponsor submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related

materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Conditional Approval

In particular circumstances, European Union legislation (Article 14–a Regulation (EC) No 726/2004 (as amended by Regulation (EU) 2019/5 and Regulation (EC) No 507/2006 on Conditional Marketing Authorizations for Medicinal Products for Human Use) enables sponsors to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for product candidates (including medicines designated as orphan medicinal products) if (1) the product candidate is intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases; (2) the product candidate is intended to meet unmet medical needs of patients; (3) a marketing authorization may be granted prior to submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required; (4) the risk-benefit balance of the product candidate is positive, and (5) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization, but applicants can also request EMA to conduct an accelerated assessment, for instance in cases of unmet medical needs.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the European Union Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the European Union Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one further five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the European Union market (in case of centralized procedure) or on the market of the authorizing European Union Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Regulatory Requirements after a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the European Union is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the European Union's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.

- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable European Union laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with European Union cGMP standards when manufacturing medicinal products and active pharmaceutical

ingredients, including the manufacture of active pharmaceutical ingredients outside of the European Union with the intention to import the active pharmaceutical ingredients into the European Union.

- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union notably under Directive 2001/83EC, as amended, and European Union Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the European Union.

Regulatory Data Protection in the European Union

In the European Union, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance the centralized authorization procedure. Data exclusivity prevents sponsors for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic marketing authorization application 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 which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Pediatric Exclusivity

If a sponsor obtains a marketing authorization in all European Union Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate, or SPC, or alternatively a one year extension of the regulatory market exclusivity from ten to eleven years, as selected by the marketing authorization holder.

Patent Term Extensions

The European Union also provides for patent term extension through 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. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained. 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.

Reimbursement and Pricing of Prescription Pharmaceuticals

In the European Union, similar political, economic and regulatory developments to those in the United States may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the United States and the European Union, reimbursement and healthcare payment systems vary significantly by country and many countries have instituted price ceilings on specific products and therapies. In many countries, including those of the European Union, 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, pharmaceutical firms may be required to conduct a clinical trial that compares the cost-effectiveness of the product to other available therapies.

Review and Approval of Medical Devices in the European Union

The European Union has adopted numerous directives and standards regulating, among other things, the design, manufacture, clinical trials, labeling, approval and adverse event reporting for medical devices. In the European Union, or the European Union, medical devices must comply with the Essential Requirements in Annex I to the currently applicable European Union Medical Devices Directive (Council Directive 93/42/EEC), or the Essential Requirements. Compliance with these requirements is a prerequisite to be able to affix the CE Mark of Conformity to medical devices, without which they cannot be marketed or sold in the European Economic Area, or EEA, comprised of the European Union member states plus Norway, Iceland, and Liechtenstein.

To demonstrate compliance with the Essential Requirements a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. Except for low risk medical devices, where the manufacturer can issue a CE Declaration of Conformity based on a self-assessment of the conformity of its products with the Essential Requirements, a conformity assessment procedure requires the intervention of a third-party organization designated by competent authorities of a European Union country to conduct conformity assessments, or a Notified Body. Notified Bodies are independent testing houses, laboratories, or product certifiers typically based within the European Union and authorized by the European member states to perform the required conformity assessment tasks, such as quality system audits and device compliance testing. The Notified Body would typically audit and examine the product's Technical File and the quality system for the manufacture, design and final inspection of the product before issuing a CE Certificate of Conformity demonstrating compliance with the relevant Essential Requirements.

Medical device manufacturers must carry out a clinical evaluation of their medical devices to demonstrate conformity with the relevant Essential Requirements. This clinical evaluation is part of the product's Technical File. A clinical evaluation includes an assessment of whether a medical device's performance is in accordance with its intended use, and that the known and foreseeable risks linked to the use of the device under normal conditions are minimized and acceptable when weighed against the benefits of its intended purpose. The clinical evaluation conducted by the manufacturer must also address any clinical claims, the adequacy of the device labeling and information (particularly claims, contraindications, precautions and warnings) and the suitability of related Instructions for Use. This assessment must be based on clinical data, which can be obtained from clinical studies conducted on the devices being assessed, scientific literature from similar devices whose equivalence with the assessed device can be demonstrated or both clinical studies and scientific literature.

With respect to implantable devices or devices classified as Class III in the European Union, the manufacturer must conduct clinical studies to obtain the required clinical data, unless relying on existing clinical data from similar devices can be justified. As part of the conformity assessment process, depending on the type of devices, the Notified Body will review the manufacturer's clinical evaluation process, assess the clinical evaluation data of a representative sample of the device's subcategory or generic group, or assess all the clinical evaluation data, verify the manufacturer's assessment of that data and assess the validity of the clinical evaluation report and the conclusions drawn by the manufacturer.

Even after a manufacturer receives a CE Certificate of Conformity enabling the CE mark to be placed on it products and the right to sell the products in the EEA countries, a Notified Body or a competent authority may require post-marketing studies of the products. Failure to comply with such requirements in a timely manner could result in the withdrawal of the CE Certificate of Conformity and the recall or withdrawal of the subject product from the European market.

A manufacturer must inform the Notified Body that carried out the conformity assessment of the medical devices of any planned substantial changes to the devices which could affect compliance with the Essential Requirements or the devices' intended purpose. The Notified Body will then assess the changes and verify whether they affect the product's conformity with the Essential Requirements or the conditions for the use of the devices. If the assessment is favorable, the Notified Body will issue a new CE Certificate of Conformity or an addendum to the existing CE Certificate of Conformity attesting compliance with the Essential Requirements. If it is not, the manufacturer may not be able to continue to market and sell the product in the EEA.

In the European Union, medical devices may be promoted only for the intended purpose for which the devices have been CE marked. Failure to comply with this requirement could lead to the imposition of penalties by the competent authorities of the European Union Member States. The penalties could include warnings, orders to discontinue the promotion of the medical device, seizure of the promotional materials and fines. Promotional materials must also comply with various laws and codes of conduct developed by medical device industry bodies in the European Union governing promotional claims, comparative advertising, advertising of medical devices reimbursed by the national health insurance systems and advertising to the general public.

Additionally, all manufacturers placing medical devices in the market in the European Union are legally bound to report any serious or potentially serious incidents involving devices they produce or sell to the competent authority in whose jurisdiction the incident occurred. In the European Union, manufacturers must comply with the European Union Medical Device Vigilance System. Under this system, incidents must be reported to the relevant authorities of the European Union countries, and manufacturers are required to take Field Safety Corrective Actions, or FSCAs, to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. An incident is defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient or user or of other persons or to a serious deterioration in their state of health. An FSCA may include the recall, modification, exchange, destruction or retrofitting of the device. FSCAs must be communicated by the manufacturer or its European Authorized Representative to its customers and to the end users of the device through Field Safety Notices.

The legal framework currently applicable for medical devices in the European Union was amended by Medical Devices Regulation (Regulation (EU) 2017/745) adopted in 2017, which we refer to as the MDR and which repeals and replaces the European Union Medical Devices Directive. Unlike directives, which must be implemented into the national laws of the European Economic Area, or EEA, member states, the MDR is directly applicable (i.e., without the need for adoption of EEA member State laws implementing them) in all EEA member states and is intended to eliminate current differences in the regulation of medical devices among EEA member states. The MDR, among other things, is intended to establish a uniform, transparent, predictable and sustainable regulatory framework across the EEA for medical and ensure a high level of safety and health.

The MDR became applicable on May 26, 2021 and will, among other things:

- strengthen the rules on placing devices on the market and reinforce surveillance once they are available;
- establish explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance and safety of devices placed on the market;
- improve the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number;
- set up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the European Union; and
- strengthen rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom’s withdrawal from the European Union took place on January 31, 2020. The European Union and the U.K. reached an agreement on their new partnership in the Trade and Cooperation Agreement, or the Trade and Cooperation Agreement, which was applied provisionally beginning on January 1, 2021 and which entered into force on May 1, 2021. The Trade and Cooperation Agreement focuses primarily on free trade by ensuring no tariffs or quotas on trade in goods, including healthcare products such as medicinal products. Thereafter, the European Union and the U.K. will form two separate markets governed by two distinct regulatory and legal regimes. As such, the Trade and Cooperation Agreement seeks to minimize barriers to trade in goods while accepting that border checks will become inevitable as a consequence that the U.K. is no longer part of the single market. 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 European Union 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 the body of European Union law instruments governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the European Union. The MHRA may rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure until December 31, 2023.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the European Union's General Data Protection Regulation, or GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the European Economic Area, or EEA, to the United Kingdom will remain lawful under GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the United Kingdom will be treated like an European Union member state in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the United Kingdom will be a "third country" under the GDPR unless the European Commission adopts an adequacy decision in respect of transfers of personal data to the United Kingdom. The United Kingdom has already determined that it considers all of the European Union 27 and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the European Union/EEA remain unaffected.

General Data Protection Regulation

Many countries outside of the United States maintain rigorous laws governing the privacy and security of personal information. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the EEA, and the processing of personal data that takes place in the EEA, is subject to the 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, and it imposes heightened requirements on companies that process health and other sensitive data, such as requiring in many situations that a company obtain the consent of the individuals to whom the sensitive personal data relate before processing such data. Examples of obligations imposed by the GDPR on companies processing personal data that fall within the scope of the GDPR include providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, appointing a data protection officer, providing notification of data breaches and taking certain measures when engaging third-party processors.

The GDPR also imposes strict rules on the transfer of personal data to countries outside the EEA, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the European Union-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the United States. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States. Following the withdrawal of the U.K. from the European Union, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-U.S. Privacy Shield. The EC initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results.

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 costs required to obtain FDA or other comparable regulatory approvals. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

Section 1833(t)(6) of the Social Security Act provides for temporary additional payments or "transitional pass-through payments" for certain drugs and biological agents. As originally enacted by the Balanced Budget Refinement Act of 1999, this provision required Centers for Medicare and Medicaid Services, or CMS, to make additional payments to hospitals for current orphan drugs, as designated under section 526 of the FDCA; current drugs and biological agents and brachytherapy sources used for the treatment of cancer; and current radiopharmaceutical drugs and biological products. Transitional pass-through payments are also provided for certain new drugs, devices and biological agents that were not paid for as a hospital outpatient department service as of December 31, 1996, and whose cost is "not insignificant" in relation to the Outpatient Prospective Payment System, or OPPS, payment for the procedures or services associated with the new drug, device, or biological. Under the statute, transitional pass-through payments can be made for at least two years but not more than three years.

J-Codes are part of the Healthcare Common Procedure Coding System (HCPCS) Level II set of procedure codes. These codes are used by CMS and other managed care organizations to identify drugs that ordinarily cannot be self-administered by a patient. Lacrimal ophthalmic inserts containing dexamethasone, such as DEXTENZA, have a specific and permanent J-Code, J1096, that allows for a simpler and more convenient reimbursement process versus miscellaneous J-codes. Since its launch, DEXTENZA has been payable in ASCs and HOPDs separately from ophthalmic surgery via the transitional pass-through status under the J1096 J-Code. However, the pass-through status for J1096 ended on December 31, 2022. In November 2022, as part of the annual CMS rule-making cycle, the CY 2023 OPPS rule was finalized and provided that DEXTENZA would qualify under the criteria established for non-opioid pain management drugs as a surgical supply provision. This provision allows for continued separate payment of DEXTENZA in the ASC setting for 2023 but does not require separate payment for DEXTENZA in the HOPD setting.

CPT codes are part of the HCPCS Level I set of procedure codes which consists of codes that are used to report medical services and procedures furnished by physicians. These codes are also used by CMS and other managed care organizations. Drug-eluting intracanalicular inserts, such as DEXTENZA, have a procedure-specific and permanent Category 1 CPT code, 68841, used to facilitate reimbursement for the administration of inserts into the canaliculus. In 2022, the Medicare Physician Fee Schedule, or MPFS, for the insertion of DEXTENZA into the canaliculus was $31.58 in the ASCs and $37.29 in the physician's office for unilateral insertion. In November 2022, the CY 2023 MPFS rule was finalized resulting in a marginal increase in physician payments over 2022 to $32.53 in the ASCs and $38.29 in the physician's office for unilateral insertion.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to

currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such 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 either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false 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, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

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

- the federal false statements statute 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 Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;

- the federal transparency requirements under the ACA, known as the federal Physician Payments Sunshine Act, will require certain manufacturers of drugs, devices, biologics and medical supplies to report to CMS within the HHS information related to payments and other transfers of value to physicians, other healthcare providers and teaching hospitals and physician 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, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Violations of these laws are punishable by criminal and/or civil sanctions, including, in some instances, exclusion from participation in federal and state health care programs, such as Medicare and Medicaid. Ensuring compliance is time consuming and costly. Similar healthcare laws and regulations exist in the EU and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and laws governing the privacy and security of personal information.

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 drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of drug and biologic products, limiting coverage and reimbursement for medical products and other changes to the healthcare system in the United States.

In March 2010, the United States Congress enacted the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, which, among other things, includes changes to the coverage and payment for pharmaceutical products under government healthcare programs. Other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included 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. Pursuant to the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, and subsequent legislation, these Medicare sequester reductions have been suspended and reduced through the end of June 2022, with the full 2% cut resuming thereafter. Under current legislation, the actual reductions in Medicare payments may vary up to 4%.

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 enactment of the Tax Cuts and Jobs Act of 2017, or the Tax Act, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the ACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden rescinded those orders and issued a new executive order that directs federal agencies to reconsider rules and other policies that limit access to healthcare, and consider actions that will protect and strengthen that access. Under this order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and under the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

Pharmaceutical Prices

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 include 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, has been 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 will 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 Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager, or PBM, service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act, or IRA, has been delayed by Congress to January 1, 2032.

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 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 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 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 certain product access and marketing cost disclosure and transparency measures, and, in some cases, 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, wholesale distributors, to disclose information about pricing of pharmaceuticals. 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 pharmaceutical and other healthcare programs. These measures could reduce the ultimate demand for our products, 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.

Human Capital

As of December 31, 2022, we had 274 full-time employees. The following table provides an overview of the distribution of those employees:

Department	Headcount
Research & Development	122
Sales & Marketing	99
Manufacturing	11
General & Administrative	42
Total Employees	274

We are committed to inclusion and diversity and believe that these are important elements of our culture that enables us to attract and retain a high quality workforce. As of December 31, 2022, our workforce was composed of approximately 47% female and 53% male, and approximately 18% of the workforce was non-white.

The development, attraction and retention of employees is a critical success factor for us for the execution of our business strategy and succession planning. To support the advancement of our employees, we offer training and development programs encouraging advancement from within and continue to fill our team with strong and experienced management talent. We leverage both formal and informal programs to identify, foster, and retain top talent at both the corporate and operating unit level.

We provide employee wages and benefits that we believe are competitive and consistent with the employee positions, skill levels, experience, knowledge and geographic location. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

We value the health, safety and wellbeing of our employees and their families. As an example, in response to the COVID-19 pandemic, we implemented significant changes that we determined were in the best interest of our employees, which included allowing a number of our corporate employees to work remotely, as appropriate.

Our Corporate Information

We were incorporated under the laws of the State of Delaware in 2006. Our principal executive offices are located at 24 Crosby Drive, Bedford, MA 01730, and our telephone number is (781) 357-4000. Our manufacturing is located at 36 Crosby Drive, Suite 101, Bedford, MA 01730 and our research and development operations are located at 15 Crosby Drive, Bedford, MA 01730. Our website address is www.ocutx.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. 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 access 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, including under the heading "Summary of Risk Factors" in this Annual Report, should be carefully considered. The risks and uncertainties described below are not the only ones 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 2 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 Financial Position and Need for Additional Capital

We have a history of incurring significant losses. We expect to incur losses over the next several years and may never achieve or maintain profitability.

We have a history of incurring significant losses. Our net loss was $71.0 million for the year ended December 31, 2022, primarily due to a loss from operations of $78.7 million offset by a change in fair value of a derivative liability of $13.8 million. Our net loss was $6.6 million for the year ended December 31, 2021, primarily due to a loss from operations of $78.0 million and a change in fair value of a derivative liability of $78.1 million. As of December 31, 2022, we had an accumulated deficit of $616.8 million. We have financed our operations primarily through sales of our products, private placements of our preferred stock, public offerings of our common stock, the private placement of convertible notes in the aggregate principal amount of our $37.5 million, or the Convertible Notes, and borrowings under credit facilities. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and clinical trials, and the commercialization of DEXTENZA. Although we expect to continue to generate revenue from sales of DEXTENZA, we expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year.

We anticipate we will incur substantial expenses if and as we:

- continue to commercialize DEXTENZA in the United States;
- continue to develop and expand our sales, marketing and distribution capabilities for DEXTENZA and any other products or product candidates we intend to commercialize;
- continue ongoing clinical trials for OTX-TKI (in both Australia and the United States) for the treatment of wet AMD and diabetic retinopathy and OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension;
- determine to initiate new clinical trials to evaluate our product candidates, including OTX-DED for the short-term treatment of the signs and symptoms of dry eye disease;
- conduct or support research and development activities on, and seek regulatory approvals for, DEXTENZA and OTX-TIC in specified Asian markets pursuant to our license agreement and collaboration with AffaMed Therapeutics Limited, or AffaMed;

- continue the research and development of our other product candidates;
- seek to identify and develop additional product candidates;
- seek marketing approvals for any of our product candidates that successfully complete clinical development;
- scale up our manufacturing processes and capabilities to support sales of commercial products, clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval, and expand our facilities to accommodate this scale up and any corresponding growth in personnel;
- renovate our existing facilities including research and development laboratories, manufacturing space and office space;
- maintain, expand and protect our intellectual property portfolio;
- expand our operational, financial, administrative and management systems and personnel, including personnel to support our clinical development, manufacturing and commercialization efforts;
- defend ourselves against legal proceedings;
- make investments to improve our defenses against cybersecurity and establish and maintain cybersecurity insurance;
- increase our product liability and clinical trial insurance coverage as we expand our clinical trials and commercialization efforts; and
- continue to operate as a public company.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our development expenses will increase if:

- we are required by the FDA or the other regulatory authorities to perform trials or studies in addition to those currently expected;
- there are any delays in receipt of regulatory clearance to begin our planned clinical programs;
- there are any delays in enrollment of subjects in or completion of our clinical trials or the development of our product candidates; or
- there are any delays in receiving marketing approval of any of our product candidates.

For us to become and remain profitable, we will need to continue to successfully commercialize DEXTENZA and to successfully develop and commercialize other products with significant market potential. This will require us or our current or future collaborators to be successful in a range of challenging activities, including:

- continuing to commercialize DEXTENZA in the United States, including by further developing our manufacturing, marketing, sales force, and distribution capabilities;
- completing clinical development of our product candidates, including OTX-TKI, OTX-TIC, OTX-DED, and OTX-CSI;
- obtaining marketing approval for these product candidates;

- manufacturing, marketing, selling and distributing any other products for which we obtain marketing approval;

- achieving an adequate level of market acceptance of and obtaining and maintaining coverage and adequate reimbursement from CMS and other third-party payors for our products; and

- protecting our rights to our intellectual property portfolio.

Even if we succeed in our commercialization efforts, we may never generate revenue that is sufficient to achieve profitability. We do not anticipate revenue from sales of DEXTENZA for the treatment of ocular inflammation and pain following ophthalmic surgery and ocular itching associated with allergic conjunctivitis will be sufficient for us to become profitable for several years, if ever.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our common stock and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need substantial additional funding. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or commercialization efforts.

We expect to devote substantial financial resources to our ongoing and planned activities, particularly as we continue to commercialize DEXTENZA for the treatment of ocular inflammation and pain following ophthalmic surgery and for the treatment of ocular itching associated with allergic conjunctivitis, and advance OTX-TKI, OTX-TIC, OTX-DED and OTX-CSI through clinical development. We expect to devote substantial financial resources as we conduct late-stage clinical trials for our product candidates, seek marketing approval for any such product candidate for which we obtain favorable pivotal clinical results, and commercialize any products for which we receive marketing approval. In addition, we plan to devote significant financial resources to conduct research and development of our other product candidates. Accordingly, we will need to obtain substantial additional funding to fully support our continuing and planned operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or commercialization efforts.

As of December 31, 2022, we had cash and cash equivalents of $102.3 million, outstanding debt of $25.3 million, net of unamortized discount, and $37.5 million aggregate principal amount of Convertible Notes plus accrued interest of $8.8 million. We believe that our existing cash and cash equivalents will enable us to fund our planned operating expenses, debt service obligations and capital expenditure requirements, excluding our planned pivotal clinical trials for OTX-TKI, into the middle of 2024. This estimate is based on our current operating plan which includes estimates of anticipated cash inflows from product sales and cash outflows from operating expenses but excludes expenses related to our planned pivotal clinical trials for OTX-TKI as we do not intend to initiate such trials without receipt of additional funding, which could be provided through a strategic collaboration. These estimates are subject to various assumptions including those related the commercialization of DEXTENZA, the pace of our research and clinical development programs and other aspects of our business. Our assumptions may prove to be wrong, and we could use our capital resources sooner than we currently expect and would therefore need to raise additional capital sooner or adjust our plans accordingly. Our future capital requirements will depend on many factors, including:

- the level of product sales from DEXTENZA and any additional products for which we obtain marketing approval in the future and the level of third-party reimbursement of such products;

- the costs of sales, marketing, distribution and other commercialization efforts with respect to DEXTENZA and any additional products for which we obtain marketing approval in the future, including costs increases due to inflation;

- the progress, costs and outcome of our ongoing and planned clinical trials of our product candidates, in particular OTX-TKI for the treatment of wet AMD and diabetic retinopathy and OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension;

- the scope, progress, costs and outcome of preclinical development and clinical trials of our other product candidates;

- the costs, timing and outcome of regulatory review of our product candidates by the FDA, the EMA or other regulatory authorities;

- the costs of scaling up our manufacturing processes and capabilities to support sales of commercial products, clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval and of expanding our facilities to accommodate this scale up and any corresponding growth in personnel;

- 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 amounts we are entitled to receive, if any, as reimbursements for clinical trial expenditures, development, regulatory, and sales milestone payments, and royalty payments under our license agreement with AffaMed;

- the extent to which we choose to establish additional collaboration, distribution or other marketing arrangements for our products and product candidates;

- the costs and outcomes of any legal actions and proceedings;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and

- the extent to which we acquire or invest in other businesses, products and technologies.

Conducting preclinical testing and clinical trials, seeking market approvals and commercializing products are time-consuming, expensive and uncertain processes that take years to complete. We may never generate the necessary data or results required to obtain regulatory approval of products with the market potential sufficient to enable us to generate significant revenues from the sale of such products. Accordingly, we will need to obtain substantial additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

Until such time, if ever, as we can generate product revenues sufficient to achieve profitability, we expect to finance our cash needs through equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements, royalty agreements, and marketing and distribution arrangements. We do not have any committed external source of funds, although our license agreement with AffaMed provides for AffaMed's reimbursement of certain clinical expenses incurred by us in connection with our collaboration and for our potential receipt of development and sales milestone payments and royalty payments. To the extent that we raise additional capital through the sale of equity, preferred equity or convertible debt securities, our stockholders' ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our existing stockholders' rights as holders of our common stock. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. Our pledge of our assets as collateral to secure our obligations under our Credit Facility pursuant to which we have a total borrowing capacity of $25.0 million, which has been fully drawn down, may limit our ability to obtain additional debt financing.

If we raise additional funds through collaborations, strategic alliances, licensing arrangements, royalty agreements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs, 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 or other arrangements when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or

grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Our substantial indebtedness may limit cash flow available to invest in the ongoing needs of our business or otherwise affect our operations.

Under our credit facility, or the Credit Facility, we have $25.0 million, net of unamortized discount, of outstanding principal indebtedness. Under the accompanying credit and security agreement, as amended and/or restated to date, which we refer to as the Credit Agreement, we are permitted to make interest-only payments through April 2024, at which time we will be required to make, in addition to the monthly interest payments, principal payments on the term loans in accordance with the Credit Agreement. Our obligations under the Credit Agreement are secured by all of our assets, including our intellectual property. The Credit Agreement also includes customary affirmative and negative covenants, including limitations on dispositions, mergers or acquisitions; incurring indebtedness, liens or encumbrances; paying dividends; making certain investments; and engaging in certain other business transactions. In March 2019, we issued $37.5 million aggregate principal amount of issued and outstanding Convertible Notes. The Convertible Notes mature on March 1, 2026 and interest on the Convertible Notes is payable at maturity or if earlier converted, repurchased or redeemed pursuant to their terms. We could in the future incur additional indebtedness beyond such amounts, including by potentially amending our Credit Agreement.

Our substantial 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 and cash equivalents and marketable securities to the payment of interest on, and principal of, our debt, which would reduce the amounts available to fund operating expenditures, including working capital, and capital expenditures and other general corporate purposes;

- obligating us to additional negative covenants further restricting our activities;

- 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 and cash equivalents, anticipated product revenue from DEXTENZA 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 our existing debt. Funds from external sources may not be available on acceptable terms, if at all.

A failure to comply with conditions of our Credit Agreement or the Convertible Notes could result in an event of default under those instruments. The Credit Agreement and Convertible Notes also have cross-default provisions, pursuant to which a default under one instrument could cause a default in others. In an event of default, including upon the occurrence of an event that would reasonably be expected to have a material adverse effect on our business or operations, the amounts due under our Credit Agreement or the Convertible Notes could accelerate. As a result, we may not have sufficient funds or may be unable to arrange for additional financing to repay our indebtedness or to make any accelerated payments, and the lenders could seek to enforce security interests in the collateral securing such indebtedness.

The elimination of LIBOR could adversely affect our business, results of operations or financial condition.

In July 2017, the head of the United Kingdom Financial Conduct Authority, or FCA, announced plans to phase out the use of LIBOR by the end of 2021. In November 2020, the International Exchange Benchmark Administration, the administrator of LIBOR, announced its decision to consult on ceasing the publication of rates for certain short-term LIBOR tenors effective December 31, 2021, and for the remaining tenors effective June 30, 2023. Financial regulatory authorities including the U.S. Federal Reserve and the FCA expressed support for announcement. Although the impact is uncertain at this time, the elimination of LIBOR could have an adverse impact on our business, results of operations, or financial condition. We may incur significant expenses to amend our LIBOR-indexed loans and other applicable

financial or contractual obligations, including our Credit Facility, to a new reference rate, which may differ significantly from LIBOR. Accordingly, the use of an alternative rate could result in increased costs, including increased interest expense on our credit facilities, and increased borrowing and hedging costs in the future. At this time, no consensus exists as to what rate or rates may become acceptable alternatives to LIBOR and we are unable to predict the effect of any such alternatives on our business, results of operations or financial condition.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2022, we had net operating loss, or NOL, carryforwards for federal and state income tax purposes of $453.3 million and $322.1 million, respectively. The federal and state NOLs generated for annual periods prior to January 1, 2018 begin to expire in 2026. Our federal NOLs generated for the years ended after December 31, 2018, which amounted to a total of $327.5 million, can be carried forward indefinitely. As of December 31, 2022, we also had available research and development tax credit carryforwards for federal and state income tax purposes of $13.4 million and $7.8 million, respectively, which begin to expire in 2026 and 2025, respectively. These NOL and tax credit carryforwards could expire unused and be unavailable to offset our future income tax liabilities. Even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes because, among other reasons, federal tax rates and the rules governing NOL carryforwards might change; state NOLs generated in one state cannot be used to offset income generated in another state; and the use of NOL carryforwards might become subject to annual limitations under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, and similar state provisions.

Risks Related to Product Development

Clinical trials of our product candidates may not be successful. If clinical trials of our product candidates fail to demonstrate safety and efficacy to the satisfaction of the FDA or other regulatory authorities or do not otherwise produce favorable results, we may incur additional costs or experience delays in completing, or ultimately be delayed or unable to complete, the development and commercialization of such product candidate and our business may be harmed.

Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. 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 stage clinical trials, interim results of a clinical trial do not necessarily predict final results and results from one completed clinical trial may not be replicated in a subsequent clinical trial with a similar study design. Some of our completed studies were conducted with small patient populations, making it difficult to predict whether the favorable results that we observed in such studies will be repeated in larger and more advanced clinical trials. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. The protocols for our clinical trials and other supporting information are subject to review by the FDA and regulatory authorities outside the United States. However, the FDA is not obligated to comment on our trial protocols within any specified time period or at all or to affirmatively clear or approve our planned pivotal clinical trials. Subject to a waiting period of 30 days, we could choose to initiate our pivotal clinical trials in the United States without waiting for any additional period for comments from the FDA.

We have devoted a significant portion of our financial resources and business efforts to the development of DEXTENZA and our product candidates. We are currently investing substantial resources to advance the development of OTX-TKI for the treatment of wet AMD and diabetic retinopathy, OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension, OTX-CSI for the chronic treatment of dry eye disease, and OTX-DED for the short-term treatment of the signs and symptoms of dry eye disease. We currently have several ongoing clinical trials, including our Phase 1 clinical trials of OTX-TKI in Australia and the United States and our Phase 2 clinical trial of OTX-TIC.

We have, however, experienced the uncertainty of clinical trials in our own development programs. In our Phase 2 clinical trial for OTX-CSI for the treatment of dry eye disease, for example, OTX-CSI did not meet the primary endpoint

of the clinical trial. The trial was designed to evaluate safety, tolerability, durability, and efficacy of two different formulations of OTX-CSI by measuring signs and symptoms of dry eye disease in 140 subjects treated in both eyes over approximately 16 weeks (a 12-week study period, with an additional 4-week safety follow-up). The four groups evaluated in this study were: OTX-CSI for a shorter duration, OTX-CSI for a longer duration, vehicle insert for a longer duration and vehicle insert for a very short duration. The study did not show separation between the OTX-CSI treated subjects (both formulations) and the vehicle treated subjects (both formulations) for the primary endpoint of increased tear production at 12 weeks as measured by the Schirmer's Test.

If clinical trials of any product candidate that we develop fail to demonstrate safety and efficacy to the satisfaction of the FDA or other regulatory authorities or do not otherwise produce clear or favorable results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of such product candidate. We cannot accurately predict when or if any of our product candidates will prove effective or safe in humans or whether our product candidates will receive marketing approval or reach successful commercialization. Our ability to generate product revenues sufficient to achieve profitability will depend heavily on our development and commercialization of products with significant market potential.

If we experience any of a number of possible unforeseen events in connection with our clinical trials, potential marketing approval or commercialization of our product candidates could be delayed or prevented.

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

- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of subjects required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their obligations to us in a timely manner, or at all;
- regulators or institutional review boards 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 trial sites;
- we may decide, or regulators or institutional review boards may require us, to suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate; and
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate.

From time to time, we may decide to conduct clinical trials to assess subjects' clinical response to treatment and choose not to power such trials to measure the applicable efficacy endpoints with statistical significance, as we did in our Phase 2 clinical trials of our former product candidate OTX-TP for the treatment of open-angle glaucoma or ocular hypertension. In addition, post-hoc analyses such as those that we performed on certain results of Phase 2 clinical trials of OTX-TP may not be predictive of success in future clinical trials, including as a result of differences in trial design. Post-hoc analyses performed using an unlocked clinical trial database can also result in the introduction of bias and are given less weight by regulatory authorities than pre-specified analyses.

The FDA may also require that NDA submissions for our product candidates include pediatric data.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, such as the FDA's requirement that we provide pediatric data for DEXTENZA for the treatment of post-surgical ocular inflammation and pain following cataract surgery prior and for the treatment of ocular itching associated with allergic conjunctivitis in connection with the approval of our NDA for DEXTENZA for those indications, 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 favorable or are only modestly favorable or if there are safety concerns, we may:

- be delayed in obtaining or unable to obtain marketing approval for our product candidates;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in testing or marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates.

If we experience delays or difficulties in the enrollment of subjects in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates or other product candidates that we might develop if we are unable to locate and enroll a sufficient number of eligible subjects to participate in these trials as required by the FDA, the EMA or similar regulatory authorities outside the United States. Although there is a significant prevalence of disease in the areas of ophthalmology in which we are focused, we may nonetheless experience unanticipated difficulty with subject enrollment. For example, in the third quarter of 2017, we initiated a Phase 1 clinical trial of OTX-TIC outside the United States. After several months, after not enrolling any subjects, we closed this trial in the second quarter of 2018. Additionally, we intended to initiate our ongoing Phase 1 clinical trial of OTX-TKI outside the United States in 2018, but delays in enrollment prevented us from dosing subjects until the first quarter of 2019.

A variety of factors affect subject enrollment, including:

- the prevalence and severity of the ophthalmic disease or condition under investigation;
- the eligibility criteria for the study in question;
- the perceived risks and benefits of the product candidate under study;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective subjects;
- actual or threatened public health emergencies or outbreaks of disease (including, for example, the COVID-19 pandemic);

- the conduct of clinical trials by competitors for product candidates that treat the same indications as our product candidates; and

- the lack of adequate compensation for prospective subjects.

Delays can be more pronounced with later-stage clinical trials because they tend to be larger than early-stage trials. For example, enrollment in our ongoing Phase 3 clinical trial to evaluate DEXTENZA in pediatric subjects following cataract surgery, to fulfill FDA post-approval regulatory requirements, is proceeding slowly due to the relative scarcity of pediatric cataract surgical subjects.

Our inability to enroll a sufficient number of subjects in any of our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which could cause the value of our common stock to decline and limit our ability to obtain additional financing.

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

If any of our product candidates are associated with serious adverse events or undesirable side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the serious adverse events, undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

Many compounds that initially showed promise in clinical or early-stage testing for treating ophthalmic disease have later been found to cause side effects that prevented further development of the compound. In addition, adverse events which had initially been considered unrelated to the study treatment may later be found to be caused by the study treatment.

We may not be successful in our efforts to develop additional products and product candidates based on our bioresorbable hydrogel technology platform.

We are currently directing most of our development efforts towards applying our proprietary, bioresorbable hydrogel technology platform to products and product candidates that are designed to provide local programmed-release hydrogel-based therapeutic agents to the eye using active pharmaceutical ingredients that are currently used in FDA-approved ophthalmic drugs. We have a number of product candidates at various stages of development based on our bioresorbable hydrogel technology platform and are exploring the potential use of our platform for other ophthalmic diseases and conditions. These product candidates include intracanalicular inserts eluting drug product to the ocular surface; hydrogel drug delivery implants designed to release therapeutic antibodies and small molecules such as TKIs to modulate the biological activity of VEGF over a sustained period following administration by an intravitreal injection for the treatment of diseases and conditions of the back of the eye, including wet AMD; and hydrogel drug delivery implants designed to release drug product into the anterior chamber of the eye via an intracameral injection for the treatment of diseases and conditions of the front of the eye.

Our product candidates and any other product candidates that we may develop based on our platform may not be suitable for continued preclinical or clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize products and product candidates that are based on our platform, we will not be able to obtain substantial product revenues in future periods.

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

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. In addition, if we

do not accurately evaluate the commercial potential of a target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We are currently prioritizing the continued commercialization of DEXTENZA, the advancement through Phase 1 clinical development of OTX-TKI for the treatment of wet AMD and diabetic retinopathy, and the advancement through Phase 2 clinical development of OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension and are assessing the further development of OTX-DED for the short-term treatment of the signs and symptoms of dry eye disease and OTX-CSI for the chronic treatment of dry eye disease . Although we believe our prioritization of resources is currently the best use of our resources, we may not be correct.

We have conducted, and may in the future conduct, clinical trials for product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

We have conducted, and may in the future choose to conduct, one or more of our clinical trials outside the United States. We have often conducted our initial and earlier-stage clinical trials for our product candidates outside the United States. We are currently conducting a Phase 1 clinical trial for our product candidate OTX-TKI for the treatment of wet AMD in Australia. We generally plan to conduct our later stage and pivotal clinical trials of our product candidates in the United States.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates. Even if the FDA accepted such data, it could require us to modify our planned clinical trials to receive clearance to initiate such trials in the United States or to continue such trials once initiated.

Other risks inherent in conducting international clinical trials include:

- foreign regulatory requirements, differences in healthcare services, and differences in cultural customs that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple sets of foreign regulations;
- foreign exchange fluctuations;
- diminished protection of intellectual property in some countries; and
- political and economic risks relevant to foreign countries.

Risks Related to Commercialization

We depend heavily on the success of DEXTENZA and any product candidates for which we may obtain marketing approval. If we fail to commercialize these products successfully, our ability to generate significant product revenues and our business would be materially harmed.

The commercial success of DEXTENZA and any other product candidate for which we obtain marketing approval will depend on many factors, including the following:

- successful completion of preclinical studies and clinical trials;

- applying for and receiving and maintaining marketing approvals from applicable regulatory authorities;
- scaling up our manufacturing processes and capabilities to support commercialization efforts;
- developing, validating and maintaining a commercially viable manufacturing process that is compliant with current good manufacturing practices, or cGMP;
- developing our sales, marketing and distribution capabilities and launching commercial sales of our products, if and when approved, whether alone or in collaboration with others;
- partnering successfully with our current and future collaborators;
- gaining acceptance of our products, if and when approved, by patients, the medical community and third-party payors, competing effectively with other therapies, and obtaining and maintaining coverage and adequate reimbursement from third-party payors;
- maintaining a continued acceptable safety profile of our products following approval; and
- protecting our intellectual property rights, including obtaining and maintaining patent and trade secret protection and regulatory exclusivity.

In certain cases, such as in our ongoing collaboration with AffaMed, many of these factors may be or are beyond our control, including clinical development and sales, marketing and distribution efforts. If we or our collaborators do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our products and product candidates, which would materially harm our business.

Even though DEXTENZA and ReSure Sealant have received marketing approval from the FDA and even if any of our product candidates receives marketing approval, any of these products 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 these products may be smaller than we estimate.

DEXTENZA, ReSure Sealant or any of our product candidates that receives marketing approval may fail to gain market acceptance by physicians, patients, third-party payors and others in the medical community. We commercially launched ReSure Sealant in the first quarter of 2014, DEXTENZA for the treatment of post-surgical ocular inflammation and pain in July 2019, and DEXTENZA for the treatment of ocular itching associated with allergic conjunctivitis in the first quarter of 2022, and we cannot yet accurately predict the extent to which these products will gain market acceptance and become commercially successful, if at all.

The degree of market acceptance of any of our products, or any product candidate for which we obtain marketing approval will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- our ability to offer our products for sale at competitive prices, particularly in light of the lower cost of alternative treatments;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments, including the intracanalicular insert retention rate for our intracanalicular insert products and product candidates;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of our marketing and distribution support;

- timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products together with other medications.

For example, because we have not conducted any clinical trials to date comparing the effectiveness of DEXTENZA directly to currently approved alternative treatments for post-surgical ocular inflammation and pain following cataract surgery or ocular itching associated with allergic conjunctivitis, market acceptance of DEXTENZA could be less than if we had conducted such trials, and we may not be able to achieve the market share we anticipate.

Our assessment of the potential market opportunity for DEXTENZA and our product candidates is based on 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. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. If the actual market for DEXTENZA or any of our product candidates is smaller than we expect, our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

If we are unable to establish and maintain adequate sales, marketing and distribution capabilities, we may not be successful in commercializing DEXTENZA or any product candidates if and when they are approved.

We have limited experience in the sale, marketing and distribution of drug and device products. To achieve commercial success for DEXTENZA and any product candidate for which we obtain marketing approval, we will need to establish and maintain adequate sales, marketing and distribution capabilities, either ourselves or through collaborations or other arrangements with third parties. We have built our own highly targeted, key account sales force for DEXTENZA that has focused primarily on ambulatory surgical centers, or ASCs, responsible for the largest volumes of cataract surgery.

In connection with our commercial launch of DEXTENZA for the treatment of ocular itching associated with allergic conjunctivitis, we launched a separate sales force focused on ophthalmologists' offices. We believe that certain other of our product candidates, if they are successfully developed and obtain marketing approval, would also be primarily used in the office setting. We believe the office setting offers a unique set of potential challenges. If we are unsuccessful in adapting our marketing efforts to include the office setting, our ability to commercialize DEXTENZA to its fullest potential or any future product candidates used in the office setting would be adversely affected.

Because we have not historically evaluated whether to seek regulatory approval for any of our products or product candidates outside of the United States, pending potential receipt of regulatory approval for the applicable product candidate in the United States, at this time we cannot be certain when, if ever, we will recognize revenue from commercialization of our products or product candidates in any international markets. If we decide to commercialize our products outside of the United States, we expect to utilize a variety of types of collaboration, distribution and other marketing arrangements with one or more third parties to commercialize any product of ours that receives marketing approval. These may include independent distributors, pharmaceutical companies or our own direct sales organization. For example, we intend to rely on AffaMed to commercialize DEXTENZA and OTX-TIC, if approved for marketing, in specified jurisdictions in Asia in connection with our collaboration agreement with AffaMed.

There are risks involved with both establishing our own sales, marketing and distribution capabilities and with entering into arrangements with third parties to perform these services. We may not be successful in entering into arrangements with third parties to sell, market and distribute our products or may be unable to do so on terms that are most beneficial to us. Such third parties may have interests that differ from ours. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to market, sell and distribute our products effectively. Our product revenues and our profitability, if any, under third-party collaboration, distribution or other marketing arrangements may also be lower than if we were to sell, market and distribute a product ourselves. On the other hand, recruiting and training a sales force is expensive and time-consuming and could delay any

product launch. If the commercial launch of any product or product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or lack of adequate number of physicians to use or prescribe our products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we do not establish and maintain sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing DEXTENZA or any of our product candidates.

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

The development and commercialization of new drug and device products is highly competitive. We face competition with respect to our products and product candidates, and will face competition with respect to any other product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Our products and product candidates target markets that are already served by a variety of competing products based on a number of active pharmaceutical ingredients. Many of these existing products have achieved widespread acceptance among physicians, patients and payors for the treatment of ophthalmic diseases and conditions. In addition, many of these products are available on a generic basis, and our products and product candidates may not demonstrate sufficient additional clinical benefits to physicians, patients or payors to justify a higher price compared to generic products. In many cases, insurers or other third-party payors, particularly Medicare, encourage the use of generic products. As a result, our products face, and product candidates, if approved, will face, competition from drugs based on the same or similar active pharmaceutical ingredients but that are administered in a different manner, typically through eye drops or intravitreal injections.

Because the active pharmaceutical ingredients in our products and product candidates are primarily available on a generic basis, or are soon to be available on a generic basis, competitors will be able to offer and sell products with the same active pharmaceutical ingredient as our products so long as these competitors do not infringe the patents that we license or own. For example, our licensed patents related to our intracanalicular insert products and product candidates largely relate to the hydrogel composition of the intracanalicular inserts and certain drug-release features of the inserts. As such, if a third party were able to design around the formulation and process patents that we license or own and create a different formulation using a different production process not covered by our licensed patents or patent applications, we would likely be unable to prevent that third party from manufacturing and marketing its product.

Other companies have advanced into Phase 3 clinical development biodegradable, programmed-release drug delivery product candidates that could compete with our intracanalicular insert products and product candidates. Multiple companies are exploring in early-stage development alternative means to deliver anti-VEGF and TKI products in an extended-delivery fashion to the back of the eye. There are also multiple branded, generic and over-the-counter products, in the dry eye space, including Restasis®, for increasing tear production, marketed by Allergan; Cequa™ for increasing tear production, marketed by Sun Ophthalmics in the United States; lifitegrast, for the treatment

of the signs and symptoms of dry eye disease, marketed by Novartis under the brand name Xiidra®; and off-label use of corticosteroids.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, are less expensive than our products or have better reimbursement. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

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

DEXTENZA and any product candidates for which we obtain marketing approval may become subject to unfavorable pricing regulations, third-party coverage or reimbursement practices or healthcare reform initiatives, which could harm our business.

Our ability to commercialize DEXTENZA or any product candidates that we may develop successfully will depend, in part, on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government healthcare programs, private health insurers, managed care plans 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 primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug and device companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for DEXTENZA or any other product that we commercialize and, even if they are available, the level of reimbursement may not be satisfactory.

Inadequate reimbursement may adversely affect the demand for, or the price of, DEXTENZA or any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize DEXTENZA or any product candidates for which we obtain marketing approval.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs and devices, and coverage may be more limited than the indications for which the drug is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any FDA-approved products that we develop would compromise our ability to generate revenues and become profitable.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug and device products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product or product candidate to other available therapies. Adverse pricing limitations may hinder our ability to recoup our investment in one or more products or product candidates, even if our product candidates obtain marketing approval.

DEXTENZA or any product candidate for which we obtain marketing approval in the United States or in other countries may not be considered medically reasonable and necessary for a specific indication, may not be considered cost-effective by third-party payors, coverage and an adequate level of reimbursement may not be available, and reimbursement policies of third-party payors may adversely affect our ability to sell our products and product candidates profitably. DEXTENZA is currently considered a post-surgical product, in the same fashion as eye drops. However, if DEXTENZA were instead categorized as an intra-operative product, it would not be subject to separate reimbursement in ASCs and hospital out-patient departments, or HOPDs, which could likewise limit its market acceptance.

A specific and permanent J-Code for ophthalmic inserts containing dexamethasone including DEXTENZA is in effect, and DEXTENZA currently benefits from separate payment in the ASC setting because it meets the criteria set forth for non-opioid pain management drugs as a surgical supply provision. CMS evaluates the eligibility of products such as DEXTENZA for separate payment annually, and there can be no assurance that CMS will not change the criteria applicable to non-opioid pain management drugs for 2023 or beyond. If DEXTENZA is no longer eligible for reimbursement separately from ophthalmic surgery, due to the loss of pass-through status or otherwise, our net product revenues, which currently consist primarily of DEXTENZA sales in reliance on separate reimbursement through pass-through status, would decline significantly, and our ability to generate revenues from future sales of DEXTENZA to ASCs and HOPDs for the treatment of post-surgical ocular inflammation and pain would be adversely affected.

CMS has also established the fixed reimbursement amount for Category I Current Procedural Terminology, or CPT, code 68841, the procedure code for the insertion of DEXTENZA. As this fee schedule is lower than reimbursement many physicians received under the prior Category III CPT code for DEXTENZA, physicians may have less incentive to use DEXTENZA and, as a result, our ability to continue to commercialize DEXTENZA may decrease. Additionally, CMS will review such determination as part of its annual rulemaking cycle, and such amount could be further reduced in the future. Physicians' desire to use DEXTENZA could also be adversely impacted if competitive products secure higher procedure payments for their use than DEXTENZA.

There are no assurances that we will be successful in maintaining reimbursement for DEXTENZA or of obtaining or maintaining reimbursement for any products or product candidates for which we might receive marketing approval in the future.

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

We face an inherent risk of product liability exposure related to the use of our product candidates that we develop in human clinical trials. We face an even greater risk for any products we develop and commercially sell or have sold, including DEXTENZA and ReSure Sealant. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any products or product candidates that we develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;

- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or subjects;
- loss of revenue;
- reduced time and attention of our management to pursue our business strategy; and
- the inability to commercialize any products that we develop.

We currently hold product liability insurance coverage; however these policies may not be adequate to cover all liabilities that we may incur and we may need to increase our insurance coverage as we expand our clinical trials and our sales of DEXTENZA and any product candidates for which we obtain marketing approval. 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.

Risks Related to Manufacturing

If our sole clinical and commercial manufacturing facility is damaged or destroyed or production at this facility is otherwise interrupted, our business and prospects would be negatively affected.

If our single-site manufacturing facility or the equipment in it is damaged or destroyed, we may not be able to quickly or inexpensively replace our manufacturing capacity or replace it at all. In the event of a temporary or protracted loss of this facility or equipment, we might not be able to transfer manufacturing to another facility or to a third party. Even if we could transfer our manufacturing to another facility or a third party, the shift would likely be expensive and time-consuming, particularly since any new facility would need to comply with the necessary regulatory requirements and to be inspected and qualified. We would also need FDA approval before any products manufactured at that facility could be used for commercial supply. In the case of any disruption in our manufacturing operations at this facility, we may not have sufficient quantities of our product candidates to meet our clinical trial requirements or of our product inventory to meet our commercial requirements. Such an event could delay our clinical trials or, particularly because we have sought to adopt just-in-time manufacturing practices and maintain limited commercial product inventory with our distributors, reduce our product sales.

Currently, we maintain insurance coverage against damage to our property and equipment and to cover business interruption and research and development restoration expenses. However, our insurance coverage may not reimburse us, or may not be sufficient to reimburse us, for any expenses or losses we may suffer. We may be unable to meet our requirements for DEXTENZA or any of our product candidates if there were a catastrophic event or failure of our current manufacturing facility or processes.

We will need to upgrade and expand our manufacturing facility or relocate to another facility and to augment our manufacturing personnel and processes in order to meet our business plans. If we fail to do so, we may not have sufficient quantities of our products or product candidates to meet our commercial and clinical trial requirements.

We manufacture DEXTENZA and our product candidates for use in clinical trials, research and development and commercial efforts at our single-site clinical and commercial manufacturing facility located in Bedford, Massachusetts. In order to meet our business plan, which contemplates our scaling up manufacturing processes to support the commercialization of our current products and the development and potential commercialization of our current and future product candidates, we will need to upgrade and expand our existing manufacturing facility, or relocate to another manufacturing facility; add manufacturing, quality and support personnel; ensure that new processes, systems, and facilities are qualified and validated; and ensure that any new processes and systems are consistently implemented in our facility or facilities. The upgrade and expansion of our facility, or the relocation to an additional facility, will require additional regulatory approvals including FDA audits of such new processes, systems, and facilities. In addition, it will be costly and time-consuming to expand our facility or relocate to another facility and recruit necessary additional personnel. If we are unable to expand our manufacturing facility or relocate to another facility in compliance with regulatory requirements or to hire additional necessary manufacturing personnel, we may encounter delays or additional costs in achieving our research, development and commercialization objectives, including obtaining regulatory approvals of our product candidates and meeting customer demand for our products, which could materially damage our business and financial position.

We must comply with federal, state and foreign regulations, including quality standards applicable to medical device and pharmaceutical manufacturers, such as cGMP, which are enforced by the FDA through means including its facilities inspection program and system audits and by similar regulatory authorities in other jurisdictions where we do business. These requirements include, among other things, quality control, quality systems and the maintenance of records and documentation. For example, between March 2015 and May 2018, we received multiple Form 483s from the FDA containing inspectional observations relating to inadequate procedures for documenting follow-up information pertinent to the investigation of complaints and for evaluation of complaints for adverse event reporting; process controls, analytical testing and physical security procedures related to manufacture of our drug product for stability and commercial production purposes; and procedures for manufacturing processes and analytical testing related to the manufacture of drug product for commercial production. In each of July 2016 and July 2017, we also received a Complete Response Letter, or CRL, from the FDA regarding our NDA for DEXTENZA pertaining to, among other things, the deficiencies in manufacturing processes, controls, and analytical testing identified during pre-NDA approval inspections of our manufacturing facility documented on Form 483s. In January and February 2021, the FDA requested information and records from us relating to our DEXTENZA commercial manufacturing operations and quality systems pursuant to Form 4003 in advance or in lieu of a drug inspection, which we provided. We may be subject to similar inspections, audits and other requirements in connection with subsequent applications for other product candidates or in connection with periodic, routine surveillance for products for which we have received marketing authorization.

The FDA or similar foreign regulatory authorities at any time also may implement new standards, or change their interpretation and enforcement of existing standards, for the manufacture, packaging or testing of our products. Any failure to comply with applicable regulations may result in fines and civil penalties, suspension of production, product seizure or recall, imposition of a consent decree, or withdrawal of product approval, and would limit the availability of DEXTENZA and our product candidates that we manufacture.

Any manufacturing defect or error discovered after products have been produced and distributed could result in significant consequences, including costly recall procedures, re-stocking costs, damage to our reputation and potential for product liability claims.

We expect to continue to contract with third parties for at least some aspects of the production of our products and product candidates. We also depend from time to time on single-source suppliers for certain materials used in the manufacturing of our products and product candidates. This increases the risk that we will not have sufficient quantities of our products or product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We currently rely on third parties for some aspects of the production of DEXTENZA and our product candidates for commercialization and preclinical testing and clinical trials. While we expect that our existing manufacturing facility, or additional facilities that we might be able to build, will be sufficient to meet our requirements for manufacturing DEXTENZA and any of our product candidates for which we obtain marketing approval, we may in the future need to rely on third-party manufacturers for some aspects of the manufacture of our products or product candidates.

We also depend on single-source suppliers for certain materials used in the manufacturing of our products and product candidates, including our supply of PEG, the molecule that forms the basis of our hydrogels, and other raw materials of our products and product candidates and for sterilization of the finished product. We do not have any long-term supply agreements in place for the clinical or commercial supply of any drug substances or raw materials for DEXTENZA or any of our product candidates. We purchase drug substance and raw materials, including the chemical constituents for our hydrogel, from independent suppliers on a purchase order basis. We cannot ensure that our suppliers will remain in business, have sufficient capacity or supply to meet our needs or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of single-source suppliers of raw materials and other components used in the manufacturing of our products and product candidates could expose us to several risks, including disruptions in supply, price increases or late deliveries. Any performance failure or refusal to supply drug substance or raw materials on the part of our existing or future suppliers could delay clinical development, marketing approval or commercialization of our products. If our current suppliers do not perform as we expect, we may be required to replace one or more of these suppliers. Establishing additional or replacement suppliers could take a substantial amount of time, and it may be difficult to establish replacement suppliers who meet our quality standards and applicable regulatory requirements. For example, we depend on a sole source supplier for the supply of our PEG. This sole source supplier may be unwilling or unable to supply PEG to us reliably, continuously and at the

levels we anticipate or are required by the market. Although we believe that there are a number of potential long-term replacements to our suppliers, including our PEG supplier, we may incur added costs and delays in identifying and qualifying any such replacements.

Reliance on third parties for aspects of the supply of our products and product candidates entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;
- the possible breach of an agreement by the third party; and
- the possible termination or nonrenewal of an agreement by the third party at a time that is costly or inconvenient for us.

Third-party suppliers or manufacturers may not be able to comply with our specifications, quality assurance standards, cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third parties, 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 product candidates. Further, reliance on third-party suppliers or manufacturers may adversely affect our future profit margins and our ability to commercialize any products that receive regulatory approval on a timely and competitive basis.

Risks Related to Our Dependence on Third Parties

We have entered into collaborations with third parties to develop certain product candidates, and in the future we may enter into additional collaborations for the development or commercialization of our product candidates. We may also enter into collaboration, distribution or marketing arrangements for the commercialization of DEXTENZA, ReSure Sealant, or any product candidates for which we obtain marketing approval outside of the United States. If our collaborations are not successful, we may not be able to capitalize on the market potential of these products or product candidates.

We have in the past entered into collaboration agreements with third parties, including our collaborations with AffaMed, and expect to utilize a variety of types of collaboration, distribution and other marketing arrangements with third parties to commercialize DEXTENZA, ReSure Sealant, or any of our product candidates for which we obtain marketing approval in markets outside the United States. We also may enter into arrangements with third parties to perform these services in the United States if we do not establish our own sales, marketing and distribution capabilities in the United States for such products or if we determine that such third-party arrangements are otherwise beneficial. We also may seek additional third-party collaborators for development and commercialization of product candidates. 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. 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.

Our collaboration with AffaMed poses, and any future collaborations likely will pose, a number of risks including the following:

- collaborators have significant discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of our products or product candidates that receive marketing approval or may elect not to continue or renew development or commercialization

programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

- 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;

- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of products or product candidates, might lead to additional responsibilities for us with respect to products or product candidates, or might result in litigation or arbitration, any of which would divert management attention and resources, be time-consuming and expensive;

- collaborators may not properly maintain or defend our intellectual property rights 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 potential litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable products or product candidates.

Collaboration agreements may not lead to the development or commercialization of products or product candidates in the most efficient manner, or at all. If any collaborations that we enter into do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our products or product candidates could be delayed and we may need additional resources to develop our products or product candidates. For example, our former collaborator Regeneron terminated our collaboration in August 2021. As a result of the termination, we were relieved of obligations to reimburse Regeneron for certain development costs, up to an aggregate amount of $30.0 million in certain circumstances, were Regeneron to exercise its option but also ceased to be eligible to receive (i) reimbursement from Regeneron for ongoing research and development activities, (ii) a fee upon exercise of its option, (iii) payments upon the achievement of specified development and regulatory milestones of the products developed under the collaboration, or (iv) tiered, escalating royalties on such products. All of the risks relating to product development, regulatory approval and commercialization described in this periodic report also apply to the activities of our collaborators.

Additionally, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be harmed.

If we are not able to establish additional collaborations, we may have to alter our development and commercialization plans and our business could be adversely affected.

In October 2020, we entered into a collaboration with AffaMed for the development and commercialization of DEXTENZA regarding ocular inflammation and pain following cataract surgery and ocular itching associated with allergic conjunctivitis and for OTX-TIC regarding open-angle glaucoma and ocular hypertension in specified territories in Asia. For some of our product candidates, we may decide to collaborate with pharmaceutical, biotechnology and medical device companies for the development and commercialization of one or more of our product candidates. We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to subjects, the potential of competing products, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. We may also be restricted under current or future license and collaboration agreements from entering into agreements on certain terms with potential collaborators. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. If we are unable to reach agreements with suitable collaborators on a timely basis and on acceptable terms, we may have to curtail the development of a product candidate, reduce or delay one or more development programs, or limit potential commercialization activities. If we elect to fund and undertake development or commercialization activities on our own, we will need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform.

Although the majority of our clinical development is administered and managed by our own employees, we have relied, and may continue to rely, on third parties for certain aspects of our clinical development, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

Our employees have administered and managed most of our clinical development work to date. However, we also utilize third parties, such as CROs, to conduct clinical trials of certain of our product candidates, including OTX-TKI for the treatment of wet AMD and OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension, and we may continue to do so. If we deem necessary, we may engage additional third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct or assist in our clinical trials or other clinical development work. If we are unable to enter into an agreement with a CRO or other service provider when required, our product development activities could be delayed.

Our reliance on third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices 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, even if a third party is administering certain activities. For example, in May 2020, we disclosed the receipt of interim data regarding our ongoing Phase 1 clinical trial of OTX-TKI, in Australia, for the treatment of wet AMD and other retinal diseases. We discovered, however, that our disclosures did not include complete information when we became aware in July 2020 that a clinical trial site had not entered certain data concerning these subjects into the clinical trial database in a timely manner. If we engage third parties and they do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

Risks Related to Our Intellectual Property

We may be unable to obtain and maintain patent protection for our technology and products, or the scope of the patent protection obtained may not be sufficiently broad, such that 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 impaired.

Our success depends in large part on our and our licensor's ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We and our licensor have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies, products and product candidates. Our licensed and owned patent portfolio that we believe is integral to our business includes patents with terms that extend from 2024 to 2041. Given the amount of time required for the development, testing and regulatory review of new product candidates, we may have a reduced patent exclusivity period upon approval. The patent prosecution process is expensive and time-consuming, and we may not have filed or prosecuted and 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 have failed, or may in the future fail, to identify patentable aspects of our research and development efforts before it is too late to obtain patent protection.

In some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to enforce or maintain the patents, covering technology that we license from third parties. In particular, the license agreement that we have entered into with Incept LLC, or Incept, an intellectual property holding company, which covers a significant portion of the patent rights and the technology for DEXTENZA, ReSure Sealant and our product candidates, provides that, with limited exceptions, Incept has sole control and responsibility for ongoing prosecution for certain patents covered by the license agreement. In addition, although we have a right under the Incept license to bring suit against third parties who infringe such licensed patents in our fields, other Incept licensees may also have the right to enforce these patents in their own respective fields without our oversight or control. Those other licensees may choose to enforce our licensed patents in a way that harms our interest, for example, by advocating for claim interpretations or agreeing on invalidity positions that conflict with our positions or our interest. For example, three of our licensed patents related to ReSure Sealant were invalidated and rendered unenforceable following their assertion by Integra LifeSciences Holdings Corporation, another licensee of Incept. We also have no right to control the defense of such licensed patents if their validity or scope is challenged before the U.S. Patent and Trademark Office, or USPTO, or other patent office or tribunal. Instead, we would essentially rely on our licensor to defend such challenges, and it may not do so in a way that would best protect our interests. Therefore, certain of our licensed patents and applications may not be prosecuted, enforced, defended or maintained in a manner consistent with the best interests of our business. If Incept fails to prosecute, enforce or maintain such patents, or loses rights to those patents, our licensed patent portfolio may be reduced or eliminated.

The patent position of pharmaceutical, biotechnology and medical device companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights, including our licensed patent rights, are highly uncertain. Our and our licensor's pending and future patent applications may not result in patents being issued which protect our technology or products or which effectively prevent others from commercializing competitive technologies and products. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Patents might not be issued and we may never obtain any patent protection or may only obtain substantially limited patent protection outside of the United States with respect to our products. Further, the complexity and uncertainty of European patent laws have increased in recent years. In Europe, a new unitary patent system will likely be introduced by the end of 2023, which would significantly impact European patents, including those granted before the introduction of such a system. Under the unitary patent system, European applications will soon have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court (UPC). As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation. Patents granted before the implementation of the UPC will have the option of opting out of the jurisdiction of the UPC and remaining as national patents in the UPC countries. Patents that remain under the jurisdiction of the UPC will be potentially vulnerable to a single UPC-based revocation challenge that, if successful, could invalidate the patent in all countries who are signatories to the UPC. We cannot predict with certainty the long-term effects of any potential changes.

Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we or our licensor were the first to make the inventions claimed in our licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions. Databases for patents and publications, and methods for searching them, are inherently limited so it is not practical to review and know the full scope of all issued and pending patent applications. As a result, the issuance, scope, validity, enforceability and commercial value of our licensed and owned patent rights are uncertain. Our 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. Moreover, changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

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, includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The USPTO developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. The first to file provisions limit the rights of an inventor to patent an invention if not the first to file an application for patenting that invention, even if such invention was the first invention. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. For example, the Leahy-Smith Act provides an administrative tribunal known as the Patent Trial and Appeals Board, or PTAB, that provides a venue for companies to challenge the validity of competitor patents at a cost that is much lower than district court litigation and on timelines that are much faster. Although it is not clear what, if any, long term impact the PTAB proceedings will have on the operation of our business, the results of patent challenge proceedings before the PTAB since its inception in 2013 have resulted in the invalidation of many U.S. patent claims. The availability of the PTAB as a lower-cost, faster and potentially more potent tribunal for challenging patents could therefore increase the likelihood that our own licensed and owned patents will be challenged, thereby increasing the uncertainties and costs of maintaining and enforcing them. Moreover, if such challenges occur, as indicated above, we have no right to control the defense of our licensed portfolio. Instead, we would essentially rely on our licensor to consider our suggestions and to defend such challenges, with the possibility that it may not do so in a way that best protects our interests.

We may be subject to a third-party preissuance submission of prior art to the USPTO, or become involved in other contested proceedings such as opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future products.

In the United States, the FDA does not prohibit physicians from prescribing an approved product for uses that are not described in the product's labeling. Although use of a product directed by off-label prescriptions may infringe our method-of-treatment patents, the practice is common across medical specialties, particularly in the United States, and such infringement is difficult to detect, prevent or prosecute. In addition, patents that cover methods of use for a medical device cannot be enforced against the party that uses the device, but rather only against the party that makes them. Such indirect enforcement is more difficult to achieve.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our licensed and owned patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products.

Because the active pharmaceutical ingredients in our products and product candidates are primarily available on a generic basis, or are soon to be available on a generic basis, competitors will be able to offer and sell products with the same active pharmaceutical ingredient as our products so long as these competitors do not infringe our patents or any patents that we license. These patents largely relate to the hydrogel composition and drug-release design scheme of our products. As such, if a third party were able to design around the formulation and process patents that we license and own and create a different formulation using a different production process not covered by our patents or patent applications, we would likely be unable to prevent that third party from manufacturing and marketing its product.

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

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, one of the U.S. patents covering each of such product candidates or the use thereof may be eligible for up to five years of patent term restoration under the Hatch-Waxman Act. The Hatch-Waxman Act allows a maximum of one patent to be extended per FDA-approved product. Patent term extension also may be available in certain foreign countries upon regulatory approval of our product candidates. Nevertheless, we may not be granted patent term extension either in the United States or in any foreign country 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. Moreover, the term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request.

Further, our license from Incept does not provide us with the right to control decisions by Incept or its other licensees on Orange Book listings or patent term extension decisions under the Hatch-Waxman Act. Thus, if one of our important licensed patents is eligible for a patent term extension under the Hatch-Waxman Act, and it covers a product of another Incept licensee in addition to our own product candidate, we may not be able to obtain that extension if the other licensee seeks and obtains that extension first.

If we are unable to obtain patent term extension or restoration, or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product may be shortened and our competitors may obtain approval of competing products following our patent expiration sooner, and our revenue could be reduced, possibly materially.

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

Competitors may infringe our licensed or owned patents or other intellectual property. As a result, to counter infringement or unauthorized use, we may file infringement claims, which can be expensive and time-consuming. Under the terms of our license agreement with Incept, we have the right to initiate suit against third parties who we believe infringe on the patents subject to the license. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent we have rights to is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. 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 alleging that we are infringing 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 to develop, manufacture, market and sell our products and product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. We may become party to, or threatened with, infringement litigation claims regarding our products and technology, including claims from competitors or from non-practicing entities that have no relevant product revenue and against whom our own patent portfolio may have no deterrent effect. Moreover, we may become party to future adversarial proceedings or litigation regarding our patent portfolio or the patents of third parties. Such proceedings could also

include contested post-grant proceedings such as oppositions, *inter partes* review, reexamination, interference or derivation proceedings before the USPTO or foreign patent offices. The legal threshold for initiating litigation or contested proceedings is low, so that even lawsuits or proceedings with a low probability of success might be initiated and require significant resources to defend. Litigation and contested proceedings can also be expensive and time-consuming, and our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we or our licensor can. The risks of being involved in such litigation and proceedings may increase as our products or product candidates near commercialization and as we gain the greater visibility associated with being a public company. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. We may not be aware of all such intellectual property rights potentially relating to our products or product candidates and their uses, or we may incorrectly determine that a patent is invalid or does not cover a particular product or product candidate. Thus, we do not know with certainty that any of our products or product candidates, or our commercialization thereof, does not and will not infringe or otherwise violate any third party's intellectual property.

We have been made aware by a third party of patents relating to intracanalicular inserts that may relate to, and potentially could be asserted against, our intracanalicular insert product and product candidates, including DEXTENZA. We believe that DEXTENZA does not infringe any claims of these patents. We also believe that such claims, if and to the extent they were asserted against our product candidates, would be subject to claims of invalidity. We initiated legal proceedings against one of these patents and administrative proceedings against the other two patents in order to show that DEXTENZA does not infringe the claims of these patents or that these patents are invalid. Legal proceedings related to one of these patents has been dismissed by agreement of the parties without prejudice. The USPTO decided to proceed with the administrative proceeding related to one of the patents while declining to do so for the other after determining that we had not established a reasonable likelihood that we would prevail in establishing the unpatentability of certain claims. In June 2020, for the patent for which the USPTO decided to proceed with administrative proceedings, the PTAB, after an *inter partes* review, determined that we had proven by a preponderance of the evidence that all claims of the patent at issue held by such third party were invalid. The third party appealed this decision, and in November 2021, the United States Court of Appeals for the Federal Circuit affirmed the holding of the PTAB. The period during which such third party may appeal the decision of the Court of Appeals has lapsed. We continue to believe that DEXTENZA does not infringe the claims of these patents and that, if and to the extent it were asserted against DEXTENZA, such patent would be subject to a claim of invalidity. We have become aware that the USPTO has recently issued a patent filed by this third party related to intracanalicular inserts containing dexamethasone. If this patent were asserted against DEXTENZA or other of our product candidates, we believe such patent would be non-infringed and subject to a claim of invalidity.

If we are found to infringe a third party's intellectual property rights, we could be required to cease manufacturing or commercializing the infringing product or product candidate or to obtain a license from such third party to continue developing and marketing our products and product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product containing such technology. 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 and could be forced to indemnify our customers or collaborators. A finding of infringement could also result in an injunction that prevents us from commercializing our products or product candidates or forces us to cease some of our business operations. In addition, we may be forced to redesign our products or product candidates, seek new regulatory approvals thereby causing delays, and indemnify third parties pursuant to contractual agreements. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

Our license agreement with Incept, under which we license certain portions of our patent rights and the technology for our products and product candidates, imposes royalty and other financial obligations and other substantial performance obligations on us. We also may enter into additional licensing and funding arrangements with third parties that may impose diligence, development and commercialization timelines and milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under current or future license and collaboration agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to

manufacture or market any product that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could diminish the value of our product. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

Under the terms of our license agreement with Incept, we have agreed to assign to Incept our rights in certain patent applications filed at any time in any country for which one or more inventors are under an obligation of assignment to us. These assigned patent applications and any resulting patents are included within the specified patents owned or controlled by Incept to which we receive a license under the agreement. Incept has retained rights to practice the patents and technology licensed to us under the agreement for all purposes other than for researching, designing, developing, manufacturing and commercializing products that are delivered to or around the human eye for diagnostic, therapeutic or prophylactic purposes relating to ophthalmic diseases or conditions. As a result, termination of our agreement with Incept, based on our failure to comply with this or any other obligation under the agreement, would cause us to lose a significant portion of our rights to important intellectual property or technology upon which our business depends. Additionally, the field limit of the license and the requirement that we assign to Incept our rights in certain patent applications may restrict our ability to use certain of our licensed rights to expand our business outside of the specified fields. If we determine to pursue a strategy of expanding the use of the hydrogel technology outside of the specified fields, we would need to negotiate and enter into an amendment to our existing license agreement with Incept or a new license agreement with Incept covering one or more additional such fields of use or utilize technologies that do not infringe on such licensed rights. We may not be able to obtain any such required amendment or new license or to invent or otherwise access other technology on commercially reasonable terms or at all.

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

Many of our employees were previously employed at universities or other biotechnology, medical device or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these employees or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee'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 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 develops intellectual property that we regard as our own, such agreements may be ineffective, or such agreements may be breached by our counterparty.

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 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 compromise our ability to compete in the marketplace.

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 our technology, products and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. 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 are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

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

Even if we complete the necessary preclinical studies and clinical trials, the regulatory 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 or any current or future collaborator of ours is not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

The activities associated with the development and commercialization of our products and product candidates, including design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States and by the EMA and similar regulatory authorities outside the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have only received approval to market DEXTENZA and ReSure Sealant in the United States, and have not received approval to market any of our product candidates or to market DEXTENZA or ReSure Sealant in any jurisdiction outside the United States. Further, we have only received approval to market DEXTENZA for the treatment of ocular inflammation and pain following ophthalmic surgery and ocular itching associated with allergic conjunctivitis. If we are unable to obtain a CE Certificate of Conformity for any of our products or product candidates for which we seek European regulatory approval, we will be prohibited from commercializing such product or products in the European Union and other places which require the CE Certificate of Conformity. In such a case, the potential market to commercialize our products may be significantly smaller than we currently estimate.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive and may take many years, if approval is obtained at all. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and purity. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA, the EMA or other regulatory authorities may determine that our product candidates are not safe or effective, are only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use.

As part of its review of the NDA for DEXTENZA for post-surgical ocular pain, the FDA completed inspections of three sites from our two completed Phase 3 clinical trials for compliance with the study protocol and Good Clinical Practices as well as two inspections of our manufacturing facility. The FDA identified several deficiencies and issued us multiple Forms 483s and two CRLs, each of which delayed our development and commercialization efforts. We may be subject to similar inspections in the future for any of our products and 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. The FDA, the EMA and regulatory authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we or any current or future collaborator of ours ultimately obtains may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

For example, 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. 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. Similarly, the regulatory landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans might be adversely impacted.

Finally, disruptions at the FDA and other agencies may prolong the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory authorities, such as the FDA, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Accordingly, if we or any current or future collaborator of ours experiences delays in obtaining approval or if we or they fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Even if we, or any current or future collaborators, obtain marketing approvals for our product candidates, the terms of approvals, ongoing regulations and post-marketing restrictions for our products may limit how we manufacture and market our products, which could materially impair our ability to generate revenue.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We, and any current or future collaborators, must therefore comply with requirements concerning advertising and promotion for any of our products for which we or our collaborators obtain marketing approval. Promotional communications with respect to drug products, biologics, and medical devices are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, if any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our product, which could limit sales of the product.

The FDA required two post-approval studies as a condition for approval of our premarket approval application for ReSure Sealant, the last of which the FDA confirmed was complete in April 2021. The studies were expensive, required extensive communication and coordination with the FDA, and took more than five years to complete. The FDA is currently requiring us to conduct a clinical trial of DEXTENZA for the treatment of post-surgical ocular inflammation and pain and for the treatment of ocular itching associated with allergic conjunctivitis in pediatric populations in accordance with the Pediatric Research Equity Act of 2003.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs applicable to drug and biologic manufacturers or quality assurance standards applicable to medical device manufacturers, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, any contract manufacturers we may engage in the future, our current or future collaborators and their contract manufacturers will also be subject to other regulatory requirements, including submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements regarding the distribution of samples to physicians, recordkeeping, and costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product such as the requirement to implement a risk evaluation and mitigation strategy.

Accordingly, in connection with our currently approved products and assuming we, or any current or future collaborators, receive marketing approval for one or more of our product candidates, we, and any current or future collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we, and any current or future collaborators, are not able to comply with post-approval regulatory requirements, we, and any current or future collaborators, could have the marketing approvals for our products withdrawn by regulatory authorities and our, or any current or future collaborators', ability to market any products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

We may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products.

Any product candidate for which we obtain marketing approval will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. In addition, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy. Accordingly, if we receive marketing approval for one or more of our product candidates, we will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we fail to comply with these requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any products could be limited, which could adversely affect our ability to achieve or sustain profitability.

We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription products are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic. Violations of the Federal Food, Drug, and Cosmetic Act, or the FDCA Act, and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products 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. 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 product distribution or use of a product;

- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure or detention;
- injunctions or the imposition of civil or criminal penalties;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation; or
- litigation involving patients using our products.

Similar restrictions apply to the approval of our products in the European Union. The holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products.

Our relationships with healthcare providers, physicians and third-party payors will be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription and use of our products and any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we 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 relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered products 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 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 product manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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

Efforts to ensure that our business with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. For example, we are engaged in an ongoing effort to improve our healthcare compliance program and establish a more robust compliance infrastructure. We may fail to establish appropriate compliance measures, and even with a stronger program in place, 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 operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in other jurisdictions. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of European Union Member States and the U.K. Bribery Act 2010. Payments made to physicians in certain European Union Member States must be publicly disclosed and often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

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

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, among other things, prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any drugs for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any future collaborators, may receive for any approved drugs. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

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 ACA. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included 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 CARES Act. Pursuant to subsequent legislation, however, these Medicare sequester reductions were suspended and reduced through the end of June 2022, with the full 2% cut scheduled to resume thereafter. 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. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our products or product candidates for which we may obtain regulatory approval or the frequency with which any such product is prescribed or used. Under current legislation, the actual reductions in Medicare payments may vary up to 4%.

Since enactment of the ACA, there have been and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the 2017 Tax Act, 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. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA and therefore because the mandate was repealed as part of the 2017 Tax Act, the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and on June 17, 2021, dismissed this action after finding that the plaintiffs did not have standing to challenge the constitutionality of the ACA. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked those Executive Orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care and consider actions that will protect and strengthen that access. Under this Executive Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

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, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our

products are prescribed or 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 that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

The prices of prescription pharmaceuticals in the United States and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed.

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, reduce the costs of pharmaceuticals under Medicare and Medicaid, and reform government program reimbursement methodologies for products. 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 include 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, has been 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 will 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, 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 November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, or PBMs, unless the price reduction is required by law. The final rule would eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and PBM service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act has been delayed by Congress to January 1, 2032.

On July 9, 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The Executive Order directed the HHS to create a plan 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 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 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 were to become 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. These measures could reduce the ultimate demand for our products, 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.

In countries outside of the United States, 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 European Union, 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 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 authorities, 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 affect liability to federal and state payers and also adversely impact reported financial results of operations in the period of such restatement.

Uncertainty exists as new laws, regulations, judicial decisions, or new interpretations of existing laws, or regulations related to our calculations, price reporting or payments obligations 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 reimbursements, penalties, sanctions or fines, which could have a material adverse effect on the business, financial condition and results of operations. In addition, it is possible that future healthcare reform measures could be adopted, which could result in increased pressure on pricing and reimbursement of products and thus have an adverse impact on financial position or business operations.

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, the 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 firm 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 Medicaid or Medicare Part B, for covered outpatient drugs.

Additionally, if a pharmaceutical company overcharges the government in connection with the Federal Supply Schedules 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 False Claims Act 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 our business, financial condition, results of operations and growth prospects.

Our collaborators are also subject to similar requirements outside of the United States 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.

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

In order to market and sell our products and product candidates in the European Union and many other jurisdictions, including certain jurisdictions covered by our AffaMed collaboration, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional 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 collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in other countries. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

We expect that we will also be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States.

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

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the EU General Data Protection Regulation, or the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and it 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. In addition, the GDPR provides that European Union member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data. Similar laws and regulations have been approved, or are expected to be approved, in several jurisdictions beyond the European Union including the U.K. Data Protection Act 2018.

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 that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act, or CCPA—which went into effect on January 1, 2020—is creating similar risks and obligations as those created by GDPR, though the CCPA does currently exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects, known as the Common Rule. The CCPA also has been amended through a recent referendum in California that creates additional obligations beginning in 2023. At least two other states have adopted, and many other states are considering, similar legislation. A broad range of legislative measures also have been 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. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and 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 is rigorous and time intensive and requires significant resources and a review of our technologies, systems

and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in applicable jurisdictions. These changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our computer systems and those of our current and any future collaborators, contractors or consultants are vulnerable to damage including from computer viruses, unauthorized access, and telecommunication and electrical failures. If a material system failure, accident or security breach were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the development and commercialization of our products and product candidates could be delayed.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain products outside of the United States and require us to develop and implement costly compliance programs.

As we expand our operations outside of the United States, such as we have begun to do with our collaboration with AffaMed, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

Risks Related to Employee Matters and Managing Growth

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

We remain highly dependent on the research and development, clinical and business development expertise of our principal members of our management, scientific and clinical team, including Antony Mattessich, our President and Chief Executive Officer. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel is critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory 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 given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Risks Related to Our Common Stock

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

Provisions in our certificate of incorporation and our bylaws 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 specified provisions of our certificate of incorporation or bylaws.

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.

We have been subject to legal proceedings related to the decline in our stock price, and we could be subject to similar legal proceedings in the future, which could distract our management and could result in substantial costs or large judgments against us.

In the past, securities class action litigation has often been brought against companies following periods of volatility in the market prices of their securities.

In July 2017, we experienced a decline in our stock price following our announcement that we had received notice of the FDA's determination that it could not approve our NDA for DEXTENZA in its then present form. In 2017 and 2018, class action lawsuits were filed against us and certain of our executive officers and shareholder derivative actions were filed against certain of our executive officers and directors, and two of our investors and against the company as a nominal defendant. While these legal proceedings were ultimately resolved in our and/or the applicable defendants' favor, they were distracting and were both time-consuming and costly to defend. We may be the target of similar proceedings in the future. We also may face securities class-action litigation if we cannot obtain regulatory approvals for or if we otherwise fail to commercialize our products or product candidates successfully.

In connection with any such legal proceedings, we could incur substantial costs and such costs and any related settlements or judgments may not be covered by insurance. We could also suffer an adverse impact on our reputation and a diversion of management's attention and resources, which could cause serious harm to our business, operating results and financial condition.

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

Our stock price has been, and in the future may be, volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price at which they purchased it. The market price for our common stock may be influenced by many factors, including:

- our success in commercializing DEXTENZA and any product candidates for which we obtain marketing approval;

- the success of competitive products or technologies;

- results of clinical trials of our product candidates and the product candidates of our competitors;

- regulatory or legal developments in the United States and other countries;

- developments or disputes concerning patent applications, issued patents or other proprietary rights;

- the recruitment or departure of key scientific or management personnel;

- the results of our efforts and the efforts of our current and future collaborators to discover, develop, acquire or in-license and out-license additional products, product candidates or technologies for the treatment of ophthalmic diseases or conditions, the costs of commercializing any such products and the costs of development of any such product candidates or technologies and any potential dilution to our shareholders as a result of these efforts;

- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

- variations in our financial results or those of companies that are perceived to be similar to us;

- the ability to secure third-party reimbursement for our products or product candidates;

- market conditions in the pharmaceutical and biotechnology sectors; and

- the other factors described in this "Risk Factors" section.

Because we do not anticipate paying any cash dividends on our capital 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 capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of our Credit Agreement and any future debt agreements that we may enter into, may preclude us from paying dividends without the lenders' 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

Not Applicable.

Item 2. Properties

Our facilities consist of leased office space, laboratory space and manufacturing facilities in Bedford, Massachusetts. We occupy approximately 121,000 square feet of space. The lease for approximately 71,000 square feet of this space expires in July 2027, the lease for approximately 30,000 square feet of this space expires in March 2024, and the lease for approximately 20,000 square feet of this space expires in July 2023. In October 2022, we exercised an option under the lease scheduled to expire in July 2023 to extend it through July 2028. Under the terms of the existing lease, rent for the five-year extension period will be based on the current fair market rent for comparable space in the building and in other similar buildings in the same rental market as of August 1, 2023, the commencement date of the additional five-year term. We believe that our current facilities are suitable and adequate to meet our current needs.

Item 3. Legal Proceedings

From time to time, we may become involved in various lawsuits and legal proceedings which arise in the ordinary course of business. However, litigation is subject to inherent uncertainties, and an adverse result in these or other matters may arise from time to time that may harm our business. We are not presently a party to any material legal proceedings, nor to the knowledge of management are any material legal proceedings threatened against us.

Item 4. Mine Safety Disclosures

Not Applicable.

PART II

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

Our common stock has been publicly traded on the Nasdaq Global Market under the symbol "OCUL" since July 25, 2014.

Holders

As of February 28, 2022, there were approximately 12 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. In addition, the terms of our existing credit facility preclude us from paying cash dividends without the consent of our lenders.

Securities Authorized for Issuance under Equity Compensation Plans

The information required by this item will be set forth in the definitive proxy statement we will file in connection with our 2023 Annual Meeting of Stockholders and is incorporated by reference herein.

Recent Sales of Unregistered Securities

We did not sell any shares of our common stock, shares of our preferred stock or warrants to purchase shares of our stock, or grant any stock options or restricted stock awards, during the year ended December 31, 2022 that were not registered under the Securities Act of 1933, as amended, or the Securities Act, and that have not otherwise been described in an Annual Report on Form 10-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.

Item 6. [Reserved.]

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

The following discussion and analysis of our financial condition and results of operations should be read together with our consolidated 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 biopharmaceutical company focused on the formulation, development, and commercialization of innovative therapies for diseases and conditions of the eye using our proprietary bioresorbable hydrogel-based formulation technology. Our mission is to build an ophthalmology-focused biopharmaceutical company that capitalizes on the gaps that we believe increasingly exist in the ophthalmology sector between single product companies and large, multi-product pharmaceutical companies.

Our current products and product candidates in clinical development incorporate therapeutic agents that have previously received regulatory approval from the U.S. Food and Drug Administration, or FDA, including small molecules, into our proprietary bioresorbable hydrogel-based formulation technology, with the goal of providing local programmed release to tailor the duration and amount of drug to be delivered to the eye. We believe that our local programmed-release drug delivery technology has the potential to treat conditions and diseases of both the front and the back of the eye and can be administered through a range of different modalities including intravitreal implants, intracameral implants and intracanalicular inserts.

We are currently commercializing DEXTENZA, an intracanalicular insert for the treatment of both post-surgical ocular inflammation and pain and ocular itching associated with allergic conjunctivitis, in the United States. We also have product candidates in preclinical and clinical development:

- OTX-TKI, an axitinib intravitreal implant being developed for the treatment of wet AMD, diabetic retinopathy and other retinal diseases;
- OTX-TIC, a travoprost intracameral implant being developed for the reduction of intraocular pressure, or IOP, in patients with primary open-angle glaucoma or ocular hypertension;
- OTX-DED, a dexamethasone intracanalicular insert being developed for the short-term treatment of the signs and symptoms of dry eye disease; and
- OTX-CSI, a cyclosporine intracanalicular insert being developed for the chronic treatment of dry eye disease;
- A complement inhibitor program in preclinical development for the treatment of dry age-related macular degeneration, or dry AMD; and
- A gene delivery program in preclinical development using our hydrogel technology to control the release of vectors such as adeno-associated virus to ocular tissues for the treatment of inherited and acquired ocular diseases, including dry or wet AMD.

AffaMed License Agreement

In October 2020, we entered into a license agreement and collaboration with AffaMed Therapeutics Limited, or AffaMed, for the development and commercialization of DEXTENZA and OTX-TIC in mainland China, Hong Kong, Macau, and Taiwan; South Korea and the countries of the Association of Southeast Asian Nations. Under the terms of the agreement, we received an upfront payment of $12 million and became eligible to receive development, regulatory and commercial milestone payments and clinical development support payments of up to $91 million in the aggregate, as

well as royalties from future product sales. In the fourth quarter of 2021, we received a $1 million milestone payment upon the approval by the FDA of an sNDA for DEXTENZA to include the treatment of ocular itching associated with allergic conjunctivitis as an additional indication; in the second quarter of 2022, we received a $2 million clinical support payment in connection with dosing the first subject in a Phase 2 clinical trial evaluating OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension. Royalties are tiered and will range from the low teens to low twenty percent range. In return, we agreed to grant AffaMed exclusive rights to develop and commercialize DEXTENZA for the treatment of post-surgical inflammation and pain following ophthalmic surgery and ocular itching in patients with allergic conjunctivitis, and OTX-TIC for the reduction of elevated IOP in patients with primary open-angle glaucoma or ocular hypertension in specified Asian markets. We retain the rights to develop and commercialize DEXTENZA and OTX-TIC in all other global markets.

Financial Position

Our ability to generate product revenues sufficient to achieve profitability will depend heavily on our continued commercialization of DEXTENZA for the treatment of ocular inflammation and pain following ophthalmic surgery and for the treatment of ocular itching associated with allergic conjunctivitis, and our development and commercialization of other products with significant market potential, including OTX-TKI for the treatment of wet AMD, diabetic retinopathy and other retinal diseases, OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension, OTX-DED for the short-term treatment of the signs and symptoms of dry eye disease and OTX-CSI for the chronic treatment of dry eye disease. Since inception, we have incurred significant operating losses. Our net losses were $71.0 million, $6.6 million and $155.6 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $616.8 million.

Our total costs and operating expenses were $130.1 million, $121.6 million and $80.3 million for the years ended December 31, 2022, 2021 and 2020, respectively, including $17.0 million, $15.0 million and $7.5 million, respectively, in non-cash stock-based compensation expense. Our operating expenses have grown as we continue to commercialize DEXTENZA; pursue the clinical development of OTX-TKI, OTX-TIC, OTX-DED and OTX-CSI, develop other product candidates; and seek marketing approval for any product candidate for which we obtain favorable pivotal clinical trial results. We expect to incur substantial sales and marketing expenses in connection with the ongoing commercialization of DEXTENZA and any commercialization efforts for any other product candidate for which we may receive approval.

Although we expect to continue to generate revenue from sales of DEXTENZA, we will need to obtain substantial additional funding to support our continuing operations and the commercialization of DEXTENZA. If we are unable to raise capital or access our borrowing capacity when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts or to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us.

In April 2019, we entered into an Open Market Sale Agreement, or the 2019 Sales Agreement, with Jefferies LLC, or Jefferies, under which we could offer and sell shares of our common stock having an aggregate offering price of up to $50.0 million from time to time through Jefferies, acting as agent. In the twelve months ended December 31, 2020, we sold 2,984,381 shares of common stock under the 2019 Sales Agreement, resulting in net proceeds of approximately $14.4 million, respectively, after commissions and expenses.

In 2020, we conducted three separate underwritten public offerings. In the twelve months ended December 31, 2020, we sold in the aggregate 21,949,841 shares of common stock resulting in net proceeds of approximately $210.1 million, after commissions and expenses.

In August 2021, we and Jefferies entered into another Open Market Sale Agreement, or the 2021 Sales Agreement, under which we may offer and sell shares of our common stock having an aggregate offering price of up to $100.0 million from time to time through Jefferies, acting as agent. In connection with entering into the 2021 Sales Agreement, we and Jefferies terminated our prior Open Market Sale Agreement which we had entered into in 2019. As of March 3, 2023, we have not sold any shares of our common stock under the 2021 Sales Agreement.

All of our products and product candidates are designed to be medical-benefit “buy-and-bill” products with associated procedure codes. Products with these characteristics are designed to be attractive not only to physicians,

optometrists and patients but also to the sites of care that participate in utilization. We primarily derive our product revenues from the sale of DEXTENZA in the United States to a network of specialty distributors, who then sell DEXTENZA to ambulatory surgical centers, or ASCs; hospital out-patient departments, or HOPDs; and physicians' offices. In addition to distribution agreements with specialty distributors, we enter into arrangements with government payors that provide for government-mandated rebates and chargebacks with respect to the purchase of DEXTENZA.

In the fourth quarter of 2022, in-market unit sales figures—unit sales from specialty distributors to ASCs and HOPDs — were in excess of 31,000 billable units. During 2022, we established a rigorous hiring process to assemble an experienced sales team that has deep buy-and-bill, ophthalmology, and surgical experience. We also adjusted our discounting strategy to meet the demands of the market. In the third quarter of 2022, we implemented an off-invoice discount program whereby providers receive the discounted price immediately upon purchase, rather than having to wait until the end of the quarter for a rebate payment. During the first two months of 2023, we are seeing continued momentum with sales of in-market billable units running more than 20% ahead of 2022 levels in the same period. In 2023, we plan to launch a customer assistance program to support the expansion of DEXTENZA in-market unit sales for commercially insured patients not covered by government payors.

We believe that our existing cash and cash equivalents of $102.3 million as of December 31, 2022, will enable us to fund our planned operating expenses, debt service obligations and capital expenditure requirements, excluding our planned pivotal clinical trials for OTX-TKI, into the middle of 2024. This estimate is based on our current operating plan which includes estimates of anticipated cash inflows from DEXTENZA product sales and cash outflows from both operating expenses and capital expenditures but excludes expenses related to our planned pivotal clinical trials for OTX-TKI as we do not intend to initiate such trials without receipt of additional funding, which could be provided through a strategic collaboration. These and other assumptions upon which we have based our estimate may prove to be wrong, and we could use our capital resources sooner than we currently expect and would therefore need to raise additional capital to support our ongoing operations or adjust our plans accordingly. See "—Liquidity and Capital Resources."

Financial Operations Overview

Revenue

In June 2019, we began to recognize revenue from the sales of DEXTENZA. We also commenced sales of ReSure Sealant in the first quarter of 2014, but we have received only limited revenues from ReSure Sealant and do not expect to receive revenues in the future. Following the FDA's October 2021 approval of our sNDA, we launched DEXTENZA for the treatment of ocular itching associated with allergic conjunctivitis, our first in-office indication, in the first quarter of 2022.

As further explained under "—Revenue Recognition—Product Revenue, Net" below, we recognize revenue when we sell DEXTENZA in the United States to a network of specialty distributors, who then resell the product to ASCs and HOPDs. We refer to these resales from the specialty distributors to the ASCs and HOPDs as in-market unit sales.

For the year ended December 31, 2022, three specialty distributor customers accounted for 44%, 25% and 17% of our total revenue, and at December 31, 2022, three specialty distributor customers accounted for 52%, 24% and 15% of our total accounts receivable. No other customer accounted for more than 10% of total revenue for the year ended December 31, 2022, or accounts receivable at December 31, 2022.

For the year ended December 31, 2021, three specialty distributor customers accounted for 42%, 26% and 17% of our total revenue, and at December 31, 2021 three specialty distributor customers accounted for 42%, 26% and 21% of our total accounts receivable. No other customer accounted for more than 10% of total revenue for the year ended December 31, 2021, or accounts receivable at December 31, 2021.

For the year ended December 31, 2020, three specialty distributor customers accounted for 42%, 29% and 12% of our total revenue. No other customer accounted for more than 10% of total revenue for the year ended December 31, 2020, or accounts receivable at December 31, 2020.

Operating Expenses

Cost of Product Revenue

Cost of product revenue consists primarily of costs of DEXTENZA product revenue, which include:

- Direct materials costs;
- Royalties;
- Direct labor, which includes employee-related expenses, including salaries, related benefits and payroll taxes, and stock-based compensation expense for employees engaged in the production process;
- Manufacturing overhead costs, which includes rent, depreciation, and indirect labor costs associated with the production process;
- Transportation costs; and
- Cost of scrap material.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the development of our product candidates, which include:

- employee-related expenses, including salaries, related benefits and payroll taxes, travel and stock-based compensation expense for employees engaged in research and development, clinical and regulatory and other related functions;
- expenses incurred in connection with the clinical trials of our product candidates, including with the investigative sites that conduct our clinical trials and under agreements with contract research organizations, or CROs;
- expenses relating to regulatory activities, including filing fees paid to the FDA for our submissions for product approvals;
- expenses associated with developing our pre-commercial manufacturing capabilities and manufacturing clinical study materials;

- ongoing research and development activities relating to our core bioresorbable hydrogel technology and improvements to this technology;

- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and supplies;

- costs relating to the supply and manufacturing of product inventory, prior to approval by the FDA or other regulatory agencies of our products; and

- expenses associated with preclinical development activities.

We expense research and development costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our vendors and our clinical investigative sites.

Our direct research and development expenses are tracked on a program-by-program basis and consist primarily of external costs, such as fees paid to investigators, consultants, central laboratories and CROs in connection with our clinical trials and regulatory fees. We do not allocate employee and contractor-related costs, costs associated with our platform technology, costs related to manufacturing or purchasing clinical trial materials, and facility expenses, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified. We use internal resources in combination with third-party CROs, including clinical monitors and clinical research associates, to manage our clinical trials, monitor subject enrollment and perform data analysis for many of our clinical trials. These employees work across multiple development programs and, therefore, we do not track their costs by program.

The successful development and commercialization of our products or product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the uncertainty of:

- the scope, progress, outcome and costs of our clinical trials and other research and development activities;

- the timing, receipt and terms of any marketing approvals;

- the efficacy and potential advantages of our products or product candidates compared to alternative treatments, including any standard of care;

- the market acceptance of our products or product candidates; and

- significant and changing government regulation.

Any changes in the outcome of any of these variables with respect to the development of our product candidates in clinical and preclinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials or other testing beyond those that we currently expect or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of that product candidate. We anticipate that our research and development expenses will increase in the future as we support our continued development of our product candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, for personnel in executive, finance, information technology, human resources and administrative functions. General and administrative expenses also include insurance, facility-related costs and professional fees for legal, patent, consulting and accounting and audit services.

We anticipate that our general and administrative expenses will increase in the future as we support our continued development and commercialization of our product candidates. We also anticipate that we will continue to incur increased accounting, audit, legal, intellectual property, regulatory, compliance, director and officer insurance costs as well as investor and public relations expenses associated with being a public company.

Selling and Marketing Expenses

Selling and marketing expenses consist primarily of salaries and related costs for personnel in selling and marketing functions as well as consulting, advertising and promotion costs. Selling and marketing expenses for DEXTENZA have increased in connection with the approval of the additional indication for ocular itching associated with allergic conjunctivitis. We anticipate that our selling and marketing expenses associated with DEXTENZA will continue to increase, particularly as we support the ongoing commercialization of DEXTENZA in 2023 and beyond.

Other Income (Expense)

Interest Income. Interest income consists primarily of interest income earned on cash and cash equivalents. In each of 2022, 2021 and 2020, our interest income has not been significant due to the low rates of interest being earned on our invested balances.

Interest Expense. Interest expense is incurred on our debt. In June 2021, we amended and restated our credit and security agreement, which we refer to as our Credit Agreement, to increase the aggregate principal amount borrowed under our credit facility, which we refer to as our Credit Facility, to $25.0 million, extend the interest-only payment period to May 1, 2024, and extend the maturity date to November 2025. In the event we achieve certain milestones under the Credit Agreement, we have the right to extend through April 1, 2026.

In March 2019, we issued $37.5 million of unsecured senior subordinated convertible notes, or the 2026 Convertible Notes. The 2026 Convertible Notes accrue interest at an annual rate of 6% of the outstanding principal amount, payable in cash at maturity, on March 1, 2026, unless earlier converted, repurchased or redeemed.

Change in Fair Value of Derivative Liability. In 2019, in connection with the issuance of our 2026 Convertible Notes, we identified an embedded derivative liability, which we are required to measure at fair value at inception and then at the end of each reporting period until the embedded derivative is settled. The changes in fair value are recorded through the statement of operations and comprehensive loss and are presented under the caption change in fair value of derivative liability. Our derivative liability calculations are further described under the heading "—Critical Accounting Policies and Significant Judgments and Estimates—Derivative Liability" below.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States of America. The preparation of our consolidated financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and the disclosure of contingent assets and liabilities in our consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to revenue recognition, accrued research and development expenses and stock-based compensation. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this annual report, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Revenue Recognition

We recognize product revenue from DEXTENZA for the treatment of post-surgical ocular inflammation and pain, which we began selling to customers in June 2019, and ReSure Sealant. We have generated limited revenues from ReSure Sealant to date and do not expect significant future sales.

In November 2018, the FDA approved DEXTENZA for the treatment of ocular pain following ophthalmic surgery. We entered into a limited number of arrangements with specialty distributors in the United States to distribute DEXTENZA. Accounting Standards Codification 606 – *Revenue from Contracts with Customers*, or Topic 606, applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance arrangements and financial instruments. Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to be entitled to in exchange for those goods or services.

To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer, (ii) identify the performance obligations in the contract, (iii) determine the transaction price, (iv) allocate the transaction price to the performance obligations in the contract, and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to arrangements that meet the definition of a contract with a customer under Topic 606, including when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied. For a complete discussion of accounting for product revenue, see *Product Revenue, Net* (below).

Product Revenue, Net— We derive our product revenues from the sale of DEXTENZA in the United States to customers, which includes a limited number of specialty distributors, who then subsequently resell DEXTENZA to physicians, clinics and certain medical centers or hospitals. We also sell DEXTENZA directly to a small population of ASCs, based on individually negotiated direct distribution agreements. In addition, we enter into arrangements with health care providers and payors that provide for government mandated or privately negotiated rebates and chargebacks with respect to the purchase of DEXTENZA.

We recognize revenue on product sales when the customer obtains control of our product, which occurs at a point in time (upon delivery to the customer). We have determined that the delivery of DEXTENZA to our customers constitutes a single performance obligation. There are no other promises to deliver goods or services beyond what is specified in each accepted customer order. We have assessed the existence of a significant financing component in the agreements with our customers. The trade payment terms with our customers do not exceed one year and therefore we have elected to apply the practical expedient and no amount of consideration has been allocated as a financing component. Product revenues are recorded net of applicable reserves for variable consideration, including discounts and allowances.

Transaction Price, including Variable Consideration— Revenues from product sales are recorded at the net sales price (transaction price), which includes estimates of variable consideration for which reserves are established. Components of variable consideration include trade discounts and allowances, product returns, government chargebacks, discounts and rebates, and other incentives, such as voluntary patient assistance, and other fee-for-service amounts that are detailed within contracts between us and our customers relating to our sale of DEXTENZA. These reserves, as detailed below, are based on the amounts earned, or to be claimed on the related sales, and are classified as reductions of accounts receivable or a current liability. These estimates take into consideration a range of possible outcomes which are probability-weighted in accordance with the expected value method in Topic 606 for relevant factors such as current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the respective underlying contracts.

The amount of variable consideration which is included in the transaction price may be constrained, and is included in the net sales price, only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized under the contract will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our original estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

Trade Discounts and Allowances—We compensate (through trade discounts and allowances) our customers for sales order management, data, and distribution services. However, we have determined such services received to date are not distinct from our sale of products to the customer and, therefore, these payments have been recorded as a reduction

of revenue within the statement of operations and comprehensive loss, as well as a reduction to trade receivables, net on the consolidated balance sheets.

Product Returns— Consistent with industry practice, we generally offer customers a limited right of return for product that has been purchased from us in certain circumstances as further discussed below. We estimate the amount of our product sales that may be returned by our customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized, as well as within accrued expenses and other current liabilities, in the accompanying consolidated balance sheets. We currently estimate product return reserves using available industry data and our own sales information, including our visibility into the inventory remaining in the distribution channel. We have received minimal returns to date and believe the returns of DEXTENZA will be minimal.

Government Chargebacks— Chargebacks for fees and discounts to qualified government healthcare providers represent the estimated obligations resulting from contractual commitments to sell products to qualified U.S. Department of Veterans Affairs hospitals and 340B entities at prices lower than the list prices charged to customers who directly purchase the product from us. The 340B Drug Discount Program is a U.S. federal government program created in 1992 that requires drug manufacturers to provide outpatient drugs to eligible health care organizations and covered entities at significantly reduced prices. Customers charge us for the difference between what they pay for the product and the statutory selling price to the qualified government entity. These allowances are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue and trade receivables, net. Chargeback amounts are generally determined at the time of resale to the qualified government healthcare provider by customers, and we generally issue credits for such amounts within a few weeks of the customer's notification to us of the resale. Allowances for chargebacks consist of credits that we expect to issue for units that remain in the distribution channel inventories at each reporting period-end that we expect will be sold to qualified healthcare providers, and chargebacks that customers have claimed, but for which we have not yet issued a credit.

Government Rebates— We are subject to discount obligations under state Medicaid programs and Medicare. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included in accrued expenses and other current liabilities on the consolidated balance sheets. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. For Medicaid programs, we estimate the portion of sales attributed to Medicaid patients and record a liability for the rebates to be paid to the respective state Medicaid programs. Our liability for these rebates consists of invoices received for claims from prior quarters that have not been paid or for which an invoice has not yet been received, estimates of claims for the current quarter, and estimated future claims that will be made for product that has been recognized as revenue, but which remains in the distribution channel inventories at the end of each reporting period.

Purchaser/Provider Discounts and Rebates—We offer rebate payments for which ASCs, HOPDs and other prescribers qualify by meeting quarterly purchase volumes of DEXTENZA under our volume-based rebate program. We calculate rebate payment amounts due under this program quarterly, based on actual qualifying purchases and apply a contractual discount rate. In the third quarter of 2022, we implemented a separate off-invoice discount, or OID, rebate program whereby end-users receive the discounted price immediately upon purchase, rather than having to wait until the end of the quarter for a rebate payment. The OID amounts are generally determined at the time of resale by specialty distributors, or SDs, or direct sales to ASCs by us. We generally issue credits for such amounts within a few weeks of the SD's notification to us of the resale. We include the OID on the invoice when we sell to an ASC directly. The calculation of the accrual for all rebates is based on an estimate of claims that we expect to receive associated with product that has been recognized as revenue but also remains in the distribution channel inventories at the end of each reporting period. The adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included as an accrued expenses and other current liabilities for volume-based rebates and as a reduction of accounts receivable for OID rebates.

Other Incentives— Other incentives which we offer include voluntary patient assistance programs, such as the co-pay assistance program, which are intended to provide financial assistance to qualified commercially-insured patients with prescription drug co-payments required by payors. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that we expect to receive associated with product that has been recognized as revenue, but remains in the distribution channel inventories at the end of each reporting period. The adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the

establishment of a current liability which is included as accrued expenses and other current liabilities on the consolidated balance sheets.

Derivative Liability

The 2026 Convertible Notes allow the holders to convert all or part of the outstanding principal of their 2026 Convertible Notes into shares our common stock provided that no conversion results in a holder beneficially owning more than 19.99% of our issued and outstanding common stock. The entire embedded conversion option is required to be separated from the 2026 Convertible Notes and accounted for as a freestanding derivative instrument subject to derivative accounting. Therefore, the entire conversion option is bifurcated from the underlying debt instrument and accounted for and valued separately from the host instrument. The main input when determining the fair value of the 2026 Convertible Notes is the bond yield that pertains to the host instrument without the conversion option. The significant assumption used in determining the bond yield is the market yield movements of a comparable instrument issued as of the valuation date, which is assessed and updated each period. We measure the value of the embedded conversion option at its estimated fair value and recognize changes in the estimated fair value in other income (expense), net in the consolidated statements of operations and comprehensive loss during the period of change. The embedded conversion is recognized as a derivative liability in our consolidated balance sheet.

Results of Operations

Comparison of the Years Ended December 31, 2022 and December 31, 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021:

	Year Ended December 31,		Increase (Decrease)
	2022	2021	
		(in thousands)	
Revenue:			
Product revenue, net	$ 50,457	$ 43,522	$ 6,935
Collaboration revenue	1,037	—	1,037
Total revenue, net	51,494	43,522	7,972
Costs and operating expenses:			
Cost of product revenue	4,540	4,406	134
Research and development	53,462	50,083	3,379
Selling and marketing	39,922	35,190	4,732
General and administrative	32,224	31,880	344
Total costs and operating expenses	130,148	121,559	8,589
Loss from operations	(78,654)	(78,037)	(617)
Other income (expense):			
Interest income	798	33	765
Interest expense	(7,022)	(6,671)	(351)
Change in fair value of derivative liability	13,841	78,121	(64,280)
Other income (expense), net	(1)	1	(2)
Total other income (expense), net	7,616	71,484	(63,868)
Net loss	$ (71,038)	$ (6,553)	$ (64,485)

Gross-to-Net Deductions

We record DEXTENZA product sales net of estimated chargebacks, rebates, distribution fees and product returns. These deductions are generally referred to as gross-to-net deductions. Our total gross-to-net provisions for the years ended December 31, 2022 and 2021 were 24.9% and 25.5%, respectively, of gross DEXTENZA product sales.

Net Revenue

We generated $50.5 million of net revenue during the year ended December 31, 2022 from sales of our products, all of which was attributable to sales of DEXTENZA. We generated $43.5 million of revenue during the year ended December 31, 2021 from sales of our products, of which $42.0 million was attributable to sales of DEXTENZA and $1.5

million was attributable to sales of ReSure Sealant. The growth in revenue for DEXTENZA was due to increased market acceptance and the continued commercialization efforts during 2022.

Collaboration Revenue

We recognized $1.0 million of collaboration revenue related to the performance obligation under our license agreement with AffaMed to conduct a Phase 2 clinical trial of OTX-TIC during the year ended December 31, 2022. We recognize collaboration revenue based on a cost-to-cost method. There was no collaboration revenue during the year ended December 31, 2021.

Research and Development Expenses

	Year Ended December 31,		Increase
	2022	2021	(Decrease)
		(in thousands)	
Direct research and development expenses by program:			
OTX-TKI for diabetic retinopathy	$ 659	$ —	$ 659
OTX-TKI for wet AMD	5,296	4,464	832
OTX-TIC for glaucoma or ocular hypertension	2,835	3,127	(292)
OTX-CSI for treatment of dry eye disease	453	3,367	(2,914)
OTX-DED for the short-term treatment of the signs and symptoms of dry eye disease	328	3,963	(3,635)
DEXTENZA for post-surgical ocular inflammation and pain	1,649	1,711	(62)
DEXTENZA for ocular itching associated with allergic conjunctivitis	21	121	(100)
ReSure Sealant	—	59	(59)
Preclinical programs	1,947	875	1,072
Unallocated expenses:			
Personnel costs	25,106	20,382	4,724
All other costs	15,168	12,014	3,154
Total research and development expenses	$ 53,462	$ 50,083	$ 3,379

Research and development expenses were $53.5 million for the year ended December 31, 2022, compared to $50.1 million for the year ended December 31, 2021. The increase of $3.4 million was primarily due to an increase of $7.9 million in unallocated expenses offset by a decrease in direct research and development program expenses of $4.5 million. Unallocated research and development costs increased $7.9 million for the year ended December 31, 2022, compared to the year ended December 31, 2021 primarily due to an increase in unallocated personnel costs of $4.7 million in personnel to support our product candidates and $3.2 million in all other costs related to facilities, general lab supplies and consulting. For the year ended December 31, 2022, we incurred $11.2 million in direct research and development expenses for our product candidates compared to $16.9 million for the year ended December 31, 2021. The decrease of $5.7 million is related to timing and start of our various clinical trials for our product candidates. We expect that clinical trial expenses will be at approximately the same level for 2023 for our product candidates including for OTX-TKI for wet AMD due to the continuation of the ongoing U.S.-based Phase 1 clinical trial and our Phase 1 clinical trial in diabetic retinopathy and for OTX-TIC due to the continuation of the ongoing Phase 2 clinical trial.

Selling and Marketing Expenses

	Year Ended December 31,		Increase
	2022	2021	(Decrease)
		(in thousands)	
Personnel related (including stock-based compensation)	$ 26,679	$ 22,862	$ 3,817
Professional fees	9,077	8,074	1,003
Facility related and other	4,166	4,254	(88)
Total selling and marketing expenses	$ 39,922	$ 35,190	$ 4,732

Selling and marketing expenses were $39.9 million for the year ended December 31, 2022, compared to $35.2 million for the year ended December 31, 2021. The increase of $4.7 million was primarily due to an increase of $3.8 million in personnel costs, including stock-based compensation as the Company expanded the field-based team to support the commercialization of DEXTENZA, and an increase of $1.0 million in professional fees including consulting, trade shows, and conferences.

We expect our selling and marketing expenses to increase in 2023 and beyond as we continue to support the commercialization of DEXTENZA.

General and Administrative Expenses

	Year Ended December 31,		Increase (Decrease)
	2022	2021	
		(in thousands)	
Personnel related (including stock-based compensation)	$ 18,227	$ 16,929	$ 1,298
Professional fees	11,634	12,402	(768)
Facility related and other	2,363	2,549	(186)
Total general and administrative expenses	$ 32,224	$ 31,880	$ 344

General and administrative expenses were $32.2 million for the year ended December 31, 2022, compared to $31.9 million for the year ended December 31, 2021. The increase of $0.3 million was primarily due to an increase of $1.3 million in personnel related costs including stock-based compensation, which was partially offset by a decrease in professional fees of $0.8 million and a decrease of $0.2 million in facility related and other costs.

Other Income (Expense), Net

Other income, net was $7.6 million for the year ended December 31, 2022, compared to other income, net of $71.5 million for the year ended December 31, 2021. The change of $63.9 million, was primarily due to an unrealized gain of $13.8 million during the year ended December 31, 2022 as compared to unrealized gain of $78.1 million in December 31, 2021 due to changes in the underlying inputs of the derivative liability, primarily related to a decrease in our common stock price between the time periods between December 31, 2020 and December 31, 2021 and December 31, 2021 and December 31, 2022. We expect the change in fair value of the derivative liability will continue to fluctuate until it is settled based on the extent to which changes occur in the underlying inputs.

Comparison of the Years Ended December 31, 2021 and 2020

A discussion of changes in our results of operations during the year ended December 31, 2021 compared to the year ended December 31, 2020 has been omitted from this Annual Report on Form 10-K but may be found in "Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on February 28, 2022, which discussion is incorporated herein by reference and which is available free of charge on the SECs website at www.sec.gov.

Liquidity and Capital Resources

We have a history of incurring significant operating losses. Our net losses were $71.0 million, $6.6 million, and $155.6 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $616.8 million.

Through December 31, 2022, we have financed our operations primarily through private placements of our preferred stock, public offerings of our common stock, private placements of our convertible notes and borrowings under credit facilities, which has resulted in net proceeds of $637.2 million to us.

On June 4, 2021, which we refer to as the Closing Date, we entered into a Fourth Amended and Restated Credit and Security Agreement, or the Fourth Amendment, with MidCap Financial Trust, as administrative agent, or the Administrative Agent, and the lenders party thereto, or the Lenders, which amended and restated our Credit Agreement to refinance our Credit Facility.

Under our Credit Agreement, we have a term loan in the aggregate principal amount of approximately $20.8 million, which was rolled over from our prior borrowings under our Credit Facility, and an additional term loan in the principal amount of approximately $4.2 million. We refer to these term loans together as the Term Loans. The aggregate principal amount of the Term Loans available under the Credit Facility, or the Total Credit Facility Amount, is $25.0 million, the entirety of which was drawn at the closing of the most recent amendment to our Credit Facility in June 2021. As of December 31, 2022, the interest rate was 10.87%. Under the current terms of our Credit Facility, we are permitted to make interest-only payments on the Term Loans on a monthly basis until May 1, 2024. Thereafter, in addition to the monthly interest payments, we are required to make principal payments on the Term Loans in accordance with the amortization schedules set forth in the Credit Agreement. Remaining unpaid principal and accrued interest outstanding on the maturity date is due on the maturity date, which shall be November 30, 2025, unless we are able to provide the Administrative Agent evidence reasonably satisfactory to it, by November 15, 2025, that the outstanding principal amount of the 2026 Convertible Notes has been converted into equity interests of ours and that such indebtedness is otherwise indefeasibly satisfied in full, in which case the term is automatically extended until April 1, 2026.

As of December 31, 2022, we had cash and cash equivalents of $102.3 million, notes payable of $25.0 million face value and senior subordinated convertible notes of $37.5 million par value, plus accrued interest of $8.8 million.

Cash Flows

Based on our current plans and forecasted expenses, which includes estimates related to anticipated cash inflows from DEXTENZA product sales and cash outflows from operating expenses, we believe that our existing cash and cash equivalents, as of December 31, 2022, will enable us to fund our planned operating expenses, debt service obligations and capital expenditure requirements into the middle of 2024, excluding our planned pivotal clinical trials for OTX-TKI as we do not intend to initiate such trials without receipt of additional funding. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

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

	Year Ended December 31,		
	2022	2021	2020
		(in thousands)	
Cash used in operating activities	$ (59,603)	$ (65,550)	$ (53,554)
Cash used in investing activities	(3,715)	(1,194)	(841)
Cash provided by financing activities	1,454	2,851	228,014
Net decrease in cash and cash equivalents	$ (61,864)	$ (63,893)	$ 173,620

Operating activities. Net cash used in operating activities was $59.6 million for the year ended December 31, 2022, primarily resulting from our net loss of $71.0 million and by non-cash adjustments of $10.1 million and cash generated by changes in our operating assets and liabilities of $1.3 million. Our net loss was primarily attributed to research and development activities, selling and marketing costs and our general and administrative expenses partially offset by $51.5 million of revenue in the period. Our net non-cash charges during the year ended December 31, 2022 primarily consisted of $17.0 million in stock-based compensation, the change in fair value of the derivative liability of $13.8 million, $4.9 million of non-cash interest expense and $2.1 million of depreciation expense. Net cash generated by changes in our operating assets and liabilities during the year ended December 31, 2022 consisted primarily of an increase in operating lease liability of $2.7 million, an increase of $1.6 million in accrued expenses, an increase in deferred revenue of $1.0 million and an decrease of prepaid expenses of $0.7 million partially offset by increase in inventory of $0.7 million, decrease in accounts payable of $0.6 million and an increase of accounts receivable of $0.2 million.

Net cash used in operating activities was $65.6 million for the year ended December 31, 2021, primarily resulting from our net loss of $6.6 million and by non-cash adjustments of $56.1 million and cash used by changes in our operating assets and liabilities of $2.9 million. Our net loss was primarily attributed to research and development activities, selling and marketing costs and our general and administrative expenses partially offset by $43.5 million of revenue in the period. Our net non-cash charges during the year ended December 31, 2021 primarily consisted of the change in fair value of the derivative liability of $78.1 million, $15.0 million of stock-based compensation expense, $4.6

million of non-cash interest expense and $2.4 million of depreciation expense. Net cash used by changes in our operating assets and liabilities during the year ended December 31, 2021 consisted primarily of an increase of $8.9 million in accounts receivable partially offset by increases in accounts payable, accrued expenses and deferred revenue of $6.5 million.

Net cash used in operating activities was $53.6 million for the year ended December 31, 2020, primarily resulting from our net loss of $155.6 million, partially offset by non-cash charges of $100.9 million and cash provided by changes in our operating assets and liabilities of $1.1 million. Our net loss was primarily attributed to research and development activities, selling and marketing costs and our general and administrative expenses partially offset by $17.4 million of revenue in the period. Our net non-cash charges during the year ended December 31, 2020 primarily consisted of the change in fair value of the derivative liability of $86.2 million, $7.5 million of stock-based compensation expense, $4.4 million of non-cash interest expense and $2.8 million of depreciation expense. Net cash provided by changes in our operating assets and liabilities during the year ended December 31, 2020 consisted primarily of a $12.0 million increase in deferred revenue partially offset by a $9.7 million increase in accounts receivable.

Investing activities. Net cash used in investing activities was $3.7 million for the year ended December 31, 2022, consisting of cash used to purchase property and equipment and leasehold improvements. Net cash used in investing activities was $1.2 million for the year ended December 31, 2021, consisting of cash used to purchase property and equipment. Net cash used in investing activities was $0.8 million for the year ended December 31, 2020, consisting of cash used to purchase property and equipment.

Financing activities. Net cash provided by financing activities for the year ended December 31, 2022 was $1.5 million and consisted of proceeds from the issuance of common stock pursuant to our employee stock purchase plan of $0.9 million and proceeds from the exercise of stock options of $0.5 million.

Net cash provided by financing activities for the year ended December 31, 2021 was $2.9 million and consisted primarily of $3.7 million, net, of proceeds in borrowings under our Credit Facility, proceeds from the exercise of stock options of $2.6 million; and proceeds from the issuance of common stock pursuant to our employee stock purchase plan of $1.0 million offset by payments on notes payable of $4.2 million.

Net cash provided by financing activities for the year ended December 31, 2020 was $228.0 million and consisted primarily of proceeds from the May 2020 Offering, the October 2020 Offering and the December 2020 Offering of an aggregate of $210.0 million, net of underwriting discounts and commissions and offering expenses; proceeds from sales under the 2019 Sales Agreement of $14.4 million, net of commissions and other offering expenses; proceeds from the exercise of stock options of $2.6 million; and proceeds from the issuance of common stock pursuant to our employee stock purchase plan of $0.8 million.

Funding Requirements

We expect to continue to incur losses in connection with our ongoing activities, particularly as we advance the clinical trials of our product candidates in development and increase our sales and marketing resources to support the commercialization of DEXTENZA and the potential launch of our product candidates, subject to receiving FDA approval.

We anticipate we will incur substantial expenses if and as we:

- continue to commercialize DEXTENZA in the United States;
- continue to develop and expand our sales, marketing and distribution capabilities for DEXTENZA and any other products or product candidates we intend to commercialize;
- continue ongoing clinical trials for OTX-TKI (in both Australia and the United States) for the treatment of wet AMD OTX-TKI in the United States for the treatment of diabetic retinopathy and diabetic retinopathy OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension;
- determine to initiate new clinical trials to evaluate our product candidates, including OTX-DED for the short-term treatment of the signs and symptoms of dry eye disease;

- conduct research and development activities on, and seek regulatory approvals for, DEXTENZA and OTX-TIC in specified Asian markets pursuant to our license agreement and collaboration with AffaMed;

- continue the research and development of our other product candidates;

- seek to identify and develop additional product candidates;

- seek marketing approvals for any of our product candidates that successfully complete clinical development;

- scale up our manufacturing processes and capabilities to support sales of commercial products, clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval, and expand our facilities to accommodate this scale up and any corresponding growth in personnel;

- renovate our existing facilities including research and development laboratories, manufacturing space and office space;

- maintain, expand and protect our intellectual property portfolio;

- expand our operational, financial, administrative and management systems and personnel, including personnel to support our clinical development, manufacturing and commercialization efforts;

- defend ourselves against legal proceedings;

- make investments to improve our defenses against cybersecurity and establish and maintain cybersecurity insurance;

- increase our product liability and clinical trial insurance coverage as we expand our clinical trials and commercialization efforts; and

- continue to operate as a public company.

Based on our current plans and forecasted expenses, which includes estimates related to anticipated cash inflows from DEXTENZA product sales and cash outflows from operating expenses, we believe that our existing cash and cash equivalents, as of December 31, 2022, will enable us to fund our planned operating expenses, debt service obligations and capital expenditure requirements into the middle of 2024, excluding our planned pivotal clinical trials for OTX-TKI as we do not intend to initiate such trials without receipt of additional funding. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

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

- the level of product sales from DEXTENZA and any additional products for which we obtain marketing approval in the future and the level of third-party reimbursement of such products;

- the costs of sales, marketing, distribution and other commercialization efforts with respect to DEXTENZA and any additional products for which we obtain marketing approval in the future, including cost increases due to inflation;

- the progress, costs and outcome of our ongoing and planned clinical trials of our product candidates, in particular OTX-TKI for the treatment of wet AMD, diabetic retinopathy and OTX-TIC for the treatment of open-angle glaucoma or ocular hypertension;

- the scope, progress, costs and outcome of preclinical development and clinical trials of our other product candidates;

- the costs, timing and outcome of regulatory review of our product candidates by the FDA, the EMA or other regulatory authorities;

- the costs of scaling up our manufacturing processes and capabilities to support sales of commercial products, clinical trials of our product candidates and commercialization of any of our product candidates for which we obtain marketing approval and of expanding our facilities to accommodate this scale up and any corresponding growth in personnel;

- 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 amounts we are entitled to receive, if any, as reimbursements for clinical trial expenditures, development, regulatory, and sales milestone payments, and royalty payments under our license agreement with AffaMed;

- the extent to which we choose to establish additional collaboration, distribution or other marketing arrangements for our products and product candidates;

- the costs and outcomes of legal actions and proceedings;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and

- the extent to which we acquire or invest in other businesses, products and technologies.

Until such time, if ever, as we can generate product revenues sufficient to achieve profitability, we expect to finance our cash needs through equity offerings, debt financings, government or other third-party funding, collaborations, strategic alliances, licensing arrangements, royalty agreements, and marketing and distribution arrangements. We do not have any committed external source of funds although our license agreement with AffaMed provides for AffaMed's reimbursement of certain clinical expenses incurred by us in connection with our collaboration and for our potential receipt of development and sales milestone payments as well as royalty payments. To the extent that we raise additional capital through the sale of equity or convertible debt securities, each security holder's ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect each security holder's rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. The covenants under our existing Credit Agreement and the pledge of our assets as collateral limit our ability to obtain additional debt financing. If we raise additional funds through government or other third-party funding, collaborations, strategic alliances, licensing arrangements, royalty agreements, or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Since our inception in 2006, we have not recorded any U.S. federal or state income tax benefits for the net losses we have incurred in each year or our earned research and development tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2022, we had net operating loss, or NOL, carryforwards for federal and state income tax purposes of $453.3 million and $322.1 million, respectively. The federal and state NOLs generated for annual periods prior to January 1, 2018 begin to expire in 2026. Our federal NOLs generated for the years ended after December 31, 2018, which amounted to a total of $327.5 million, can be carried forward indefinitely. As of December 31, 2022, we also had available research and development tax credit carryforwards for federal and state income tax

purposes of $13.4 million and $7.8 million, respectively, which begin to expire in 2026 and 2025, respectively. We have not completed a study to assess whether an ownership change, generally defined as a greater than 50% change (by value) in the equity ownership of our corporate entity over a three-year period, has occurred or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such studies. Accordingly, our ability to utilize our tax carryforwards may be limited. Additionally, U.S. tax laws limit the time during which these carryforwards may be utilized against future taxes. As a result, we may not be able to take full advantage of these carryforwards for federal and state tax purposes.

Contractual Obligations and Commitments

	Total	Less Than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
			(in thousands)		
Operating lease commitments	$ 13,669	$ 2,663	5,470	4,820	716
Credit Agreement	30,619	1,994	28,625	—	—
2026 Convertible Notes	53,475	—	—	53,475	—
Total	$ 97,763	$ 4,657	$ 34,095	$ 58,295	$ 716

The table above includes our enforceable and legally binding obligations and future commitments at December 31, 2022, as well as obligations related to contracts that we are likely to continue, regardless of the fact that they may be cancelable at December 31, 2022. Some of the figures that we include in this table are based on management's estimates and assumptions about these obligations, including their duration, and other factors. Because these estimates and assumptions are necessarily subjective, the amounts we will actually pay in future periods may vary from those reflected in the table.

We enter into contracts in the normal course of business to assist in the performance of our research and development activities and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancelable contracts which are not included in contractual obligations and commitments.

Operating lease commitments represent payments due under our leases of office, laboratory and manufacturing space in Bedford, Massachusetts and certain office equipment under operating leases that expire in March 2024, July 2027, and July 2028. We expect lease costs under these commitments to total $2.7 million in 2023 and increase annually. We expect total costs of approximately $13.7 million over the terms of our current leases.

Under the Fourth Amendment, we are permitted to make interest-only payments under our Credit Facility through April 2024. Commencing in May 2024, we are required to make 19 equal monthly installments of principal in the amount of $1.0 million, plus interest, then on the maturity date, November 30, 2025 the remaining balance of $5.2 million plus the exit fee. In the event we achieve certain milestones under the Fourth Amendment, we have the right to extend through April 1, 2026 and make 5 equal monthly installments of principal in the amount of $1.0 million, plus interest. We have not assumed the achievement of these milestones in the table above.

On March 2019, we issued the 2026 Convertible Notes pursuant to a note purchase agreement, or the Purchase Agreement, with Cap 1 LLC, an affiliate of Summer Road LLC. The 2026 Convertible Notes accrue interest at an annual rate of 6% of its outstanding principal amount, payable at maturity, on March 1, 2026, unless earlier converted, repurchased or redeemed. The holders of the 2026 Convertible Notes may convert all or part of the outstanding principal amount of their 2026 Convertible Notes into shares of our common stock, par value $0.0001 per share, prior to maturity and provided that no conversion results in a holder beneficially owning more than 19.99% of our issued and outstanding common stock. The conversion rate is initially 153.8462 shares of our common stock per $1,000 principal amount of the 2026 Convertible Notes, which is equivalent to an initial conversion price is $6.50 per share. The conversion rate is subject to adjustment in customary circumstances such as stock splits or similar changes to our capitalization. At our election, we may choose to make such conversion payment in cash, in shares of common stock, or in a combination thereof. Upon any conversion of any 2026 Convertible Note, we are obligated to make a cash payment to the holder of such 2026 Convertible Note for any interest accrued but unpaid on the principal amount converted. Upon the occurrence of a Corporate Transaction (as defined in the 2026 Convertible Notes), the holder of a 2026 Convertible Note is entitled, at such holder's option, to convert all of the outstanding principal amount of the 2026 Convertible Note in accordance

with the foregoing and receive an additional, "make-whole" cash payment in accordance with a table set forth in each 2026 Convertible Note.

Upon the occurrence of a Corporate Transaction, each holder of a 2026 Convertible Note has the option to require us to repurchase all or part of the outstanding principal amount of such 2026 Convertible Note at a repurchase price equal to 100% of the outstanding principal amount of the 2026 Convertible Note to be repurchased, plus accrued and unpaid interest to, but excluding, the repurchase date.

If the last reported sale price of the common stock has been at least 130% of the conversion rate then in effect for twenty of the preceding thirty trading days (including the last trading day of such period), we are entitled, at our option, to redeem all or part of the outstanding principal amount of the 2026 Convertible Notes, on a pro rata basis, at an optional redemption price equal to 100% of the outstanding principal amount of the 2026 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the optional redemption date.

The Purchase Agreement contains customary representations and warranties by us and the noteholder. The Purchase Agreement does not include any financial covenants. Our obligations under the Purchase Agreement and the 2026 Convertible Notes are subject to acceleration upon the occurrence of specified events of default, including a default or breach of certain contracts material to us and the delisting and deregistration of our common stock.

We have in-licensed a significant portion of our intellectual property from Incept, an intellectual property holding company, under an amended and restated license agreement, or the License Agreement, that we entered into with Incept in January 2012, which was most recently amended in September 2018. We are obligated to pay Incept a royalty equal to a low-single-digit percentage of net sales made by us or our affiliates of any products, devices, materials, or components thereof, or the Licensed Products, including or covered by Original IP (as defined in the License Agreement), excluding the Shape-Changing IP (as defined in the License Agreement), in the Ophthalmic Field of Use (as defined in the License Agreement). We are obligated to pay Incept a royalty equal to a mid-single-digit percentage of net sales made by us or our affiliates of any Licensed Products including or covered by Original IP, excluding the Shape-Changing IP, in the Additional Field of Use (as defined in the License Agreement). We are obligated to pay Incept a royalty equal to a low-single-digit percentage of net sales made by us or our affiliates of any Licensed Products including or covered by Incept IP (as defined in the License Agreement) or Joint IP (as defined in the License Agreement) in the field of drug delivery. Any sublicensee of ours also will be obligated to pay Incept a royalty on net sales of Licensed Products made by it and will be bound by the terms of the agreement to the same extent as we are. We are obligated to reimburse Incept for our share of the reasonable fees and costs incurred by Incept in connection with the prosecution of the patent applications licensed to us under the agreement. Our share of these fees and costs is equal to the total amount of such fees and costs divided by the total number of Incept's exclusive licensees of the patent application. We have not included in the table above any payments to Incept under this license agreement as the amount, timing and likelihood of such payments are not known.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the Securities and Exchange Commission, such relationships with unconsolidated entities or financial partnerships, which are often referred to as structured finance or special purpose entities, established for the purpose of facilitating financing transactions that are not required to be reflected on our balance sheets.

Recently Issued Accounting Pronouncements

Information regarding new accounting pronouncements is included in Note 2 – *Summary of Significant Accounting Policies* to the current period's consolidated financial statements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2022, we had cash and cash equivalents of $102.3 million, which includes cash in operating bank accounts, investments in money market accounts, and money market funds. We have policies requiring us to invest in high-quality issuers, limit our exposure to any individual issuer, and ensure adequate liquidity. 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 our investments are in short-term securities. Due to the short-term duration of our investment portfolio and 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 do not enter into financial instruments for trading or speculative purposes.

We account for the conversion option embedded in our 2026 Convertible Notes as a separate financial instrument, measured at fair value, using a binomial lattice model, which we refer to as the Derivative Liability. As of December 31, 2022, the Derivative Liability was valued at $6.4 million. As of December 31, 2022, a 10% increase or decrease of the main inputs to the valuation model would not have a material effect on the fair value of the Derivative Liability. Changes of the fair value of the Derivative Liability have no impact on anticipated cash outflows.

As of December 31, 2022, we had a variable interest rate-based note payable with a principal amount of $25.0 million. Expected cash outflows from this financial instrument fluctuate based on changes in the U.S. dollar-denominated LIBOR index which is, among other factors, affected by the general level of U.S. and international central bank interest rates. As of December 31, 2022, an immediate 100 basis point increase or decrease in the U.S. dollar-denominated LIBOR index would not have a material effect on the anticipated cash outflows from this instrument.

Item 8. Financial Statements and Supplementary Data

Our consolidated financial statements, together with the report of our independent registered public accounting firm, appear on pages F-1 through F-33 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 Securities Exchange Act of 1934, as amended, or 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, including our Chief Executive Officer and Chief Financial Officer 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 for Ocular Therapeutix, Inc. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's 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 and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the company;

- 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

- 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.

Our management, including our President and Chief Executive Officer and Chief Financial Officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control—Integrated Framework* (2013*)*. Based on that assessment, our management concluded that, as of December 31, 2022, our internal control over financial reporting was effective.

Changes in Internal Control Over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding 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 Stockholders 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 Stockholders, if applicable, and is incorporated in this Annual Report on Form 10-K by reference.

Code of Ethics

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

Director Nominees

The information required by this item will be set forth in our Proxy Statement for the 2023 Annual Meeting of Stockholders 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 Securities Exchange Act of 1934, as amended, or 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 Stockholders and is incorporated in this Annual Report on Form 10-K by reference.

Audit Committee Financial Expert

Our board of directors has determined that Merilee Raines qualifies as an “audit committee financial expert” as defined by Item 407(d)(5) of Regulation S-K of the Exchange Act and is “independent” under the rules of the Nasdaq Global Market.

Item 11. Executive Compensation

The information required by this item will be set forth in our Proxy Statement for the 2023 Annual Meeting of Stockholders and is incorporated in this Annual Report on Form 10-K by reference.

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

The information required by this item will be set forth in our Proxy Statement for the 2023 Annual Meeting of Stockholders 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 Stockholders and is incorporated in this Annual Report on Form 10-K by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item will be set forth in our Proxy Statement for the 2023 Annual Meeting of Stockholders and is incorporated in this Annual Report on Form 10-K by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

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

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 consolidated financial statements or notes thereto.

The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following Item 16. The Exhibit Index is incorporated herein by reference.

Item 16. Form 10-K Summary

None.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-36554	7/30/2014	3.1	
3.2	Amended and Restated Bylaws of the Registrant	8-K	001-36554	7/30/2014	3.2	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1/A	333-196932	7/11/2014	4.1	
4.2	Registration Rights Agreement, dated as of March 1, 2019, by and among the Registrant and the Purchasers identified therein	10-K	001-36554	3/7/2019	4.2	
4.3	Description of Securities Registered under Section 12 of the Exchange Act	10-K	001-36554	2/28/2022	4.3	
10.1+	2006 Stock Incentive Plan, as amended	S-1	333-196932	6/20/2014	10.1	
10.2+	Form of Stock Option Agreement under 2006 Stock Incentive Plan	S-1	333-196932	6/20/2014	10.2	
10.3+	Form of Restricted Stock Agreement under 2006 Stock Incentive Plan	S-1	333-196932	6/20/2014	10.3	
10.4+	2014 Stock Incentive Plan	S-1/A	333-196932	7/11/2014	10.4	
10.5+	Form of Incentive Stock Option Agreement under 2014 Stock Incentive Plan	S-1/A	333-196932	7/11/2014	10.5	
10.6+	Form of Non-statutory Stock Option Agreement under 2014 Stock Incentive Plan	S-1/A	333-196932	7/11/2014	10.6	
10.7+	Form of Restricted Stock Agreement under 2014 Stock Incentive Plan	S-1/A	333-196932	7/11/2014	10.7	
10.8+	2019 Inducement Stock Incentive Plan	10-Q	001-036554	11/12/2019	10.1	
10.9+	Amendment to 2019 Inducement Stock Incentive Plan	10-K	001-36554	3/11/2021	10.9	
10.10+	Form of Non-statutory Stock Option Agreement under 2019 Inducement Stock Incentive Plan	10-Q	001-036554	11/12/2019	10.2	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.11†	Amended and Restated License Agreement, dated January 27, 2012, between the Registrant and Incept LLC	S-1	333-196932	6/20/2014	10.8	
10.12	Lease Agreement dated September 2, 2009, by and between the Registrant and RAR2-Crosby Corporate Center QRS, Inc., as amended.	S-1	333-196932	6/20/2014	10.9	
10.13+	2014 Employee Stock Purchase Plan	S-1/A	333-196932	7/11/2014	10.10	
10.14	Form of Indemnification Agreement by and between the Registrant and each of its directors and executive officers	S-1	333-196932	6/20/2014	10.12	
10.15	Transition, Separation and Release of Claims Agreement by and between the Registrant and Dr. Amarpreet S. Sawhney dated as of May 29, 2019	8-K	001-36554	5/30/2019	10.1	
10.16	Lease Agreement dated June 17, 2016 between the WS NF 15 Crosby Drive, LLC and the Registrant	10-Q	001-36554	8/9/2016	10.1	
10.18	Open Market Sale Agreement, dated as of August 9, 2021, by and between the Registrant and Jefferies LLC	8-K	001-36554	8/9/2021	1.1	
10.19+	Employment Agreement, by and between the Registrant and Philip Strassburger, dated August 28, 2020	10-K	001-36554	3/11/2021	10.19	
10.20	Consulting Agreement by and between the Registrant and Dr. Amarpreet S. Sawhney, dated as of May 29, 2019	8-K	001-36554	5/30/2019	10.2	
10.21+	Employment Agreement, by and between the Registrant and Antony C. Mattessich, dated as of June 20, 2017	8-K	001-36554	6/22/2017	10.2	
10.22+	Non-Statutory Stock Option Agreement, by and between the Registrant and Antony C. Mattessich dated as of June 20, 2017	8-K	001-36554	6/22/2017	10.3	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.23+	Employment Agreement, by and between the Registrant and Donald Notman, dated as of September 25, 2017	8-K	001-36554	9/25/2017	10.1	
10.24	Second Amendment to Lease, by and between the Registrant and CCC Investors LLC, dated October 10, 2017	8-K	001-36554	10/16/2017	10.1	
10.25+	Employment Agreement, by and between the Registrant and Michael Goldstein, dated as of September 25, 2017	10-K	001-36554	3/8/2018	10.30	
10.26†	Second Amended and Restated License Agreement, dated September 13, 2018, by and between the Registrant and Incept LLC	8-K	001-36554	9/19/2018	10.1	
10.27	Third Amended and Restated Credit and Security Agreement dated December 21, 2018 by and among MidCap Financial Trust, as administrative agent, the Registrant, and the Lenders listed therein	8-K	001-36554	12/28/2018	10.1	
10.28	First Amendment to Third Amended and Restated Credit and Security Agreement, dated as of February 21, 2019, by and among the Registrant, MidCap Financial Trust, as administrative agent, and the Lenders listed therein	8-K	001-36554	2/22/2019	10.3	
10.29	Second Amendment to Third Amended and Restated Credit and Security Agreement, by and among the Registrant, MidCap Financial Trust, as administrative agent, and the Lenders listed therein	10-Q	001-36554	8/7/2019	10.5	
10.30	Subordination Agreement, dated as of February 21, 2019, by and among the Registrant, MidCap Financial Trust, as administrative agent, and the Lenders listed therein	8-K	001-36554	2/22/2019	10.4	
10.31	Note Purchase Agreement (including Form of Senior Subordinated Convertible Note), dated as of February 21, 2019, by and among the Registrant and the Purchasers listed therein	8-K	001-36554	2/22/2019	10.1	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.32	Sublease, dated as of April 4, 2019, by and among Ocular Therapeutix, Inc. and Holcim (US) Inc.	10-Q	001-36554	5/10/2019	10.4	
10.35*	License Agreement, by and between the Registrant and AffaMed Therapeutics Limited, dated as of October 29, 2020	10-Q	001-36554	11/5/2020	10.1	
10.36*	Supplement to License Agreement, by and between the Registrant and AffaMed Therapeutics Limited, dated as of January 18, 2021	10-K	001-36554	3/11/2021	10.36	
10.37	Fourth Amended and Restated Credit and Security Agreement dated June 4, 2021 by and among the Registrant, MidCap Financial Trust, as administrative agent, and the Lenders listen therein	8-K	001-36554	6/4/2021	10.1	
10.38+	2021 Stock Incentive Plan, as amended	10-Q	001-36554	8/8/2022	10.1	
10.39+	Form of Option Grant Agreement under 2021 Stock Incentive Plan	10-K	001-36554	2/28/2022	10.1	
10.40+	Form of Restricted Stock Unit Agreement under 2021 Stock Incentive Plan	10-K	001-36554	2/28/2022	10.39	
10.41	Amendment No. 1 to License Agreement, by and between the Registrant and AffaMed Therapeutics (HK) Limited, dated as of October 28, 2021	10-K	001-36554	2/28/2022	10.40	
10.42	Consulting Agreement by and between the Registrant and Dr. Michael Goldstein, dated as of June 7, 2022	10-Q	001-36554	8/8/2022	10.2	
10.43	Consulting Agreement by and between the Registrant and Dr. Jeffrey Heier, dated as of October 17, 2022					X
10.44	Employment Agreement, by and between the Registrant and Rabia Ozden-Gurses, dated as of September 28, 2022					X

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.45	Employment Agreement, by and between the Registrant and Christopher White, dated as of October 13, 2022					X
21.1	Subsidiaries of the Registrant					X
23.1	Consent of PricewaterhouseCoopers LLP					X
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					X
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					X
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					X
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					X
101.INS	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document)					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Database					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
104	The cover page from this Annual Report on Form 10-K, formatted in Inline XBRL and contained in Exhibit 101					X

† 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.

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

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 6, 2023

OCULAR THERAPEUTIX, INC.

By: /s/ Donald Notman
Donald Notman
Chief Financial Officer
(Principal Financial and Accounting Officer)

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

Signature	Title	Date
/s/ Antony Mattessich Antony Mattessich	President and Chief Executive Officer (Principal Executive Officer)	March 6, 2023
/s/ Donald Notman Donald Notman	Chief Financial Officer (Principal Financial and Accounting Officer)	March 6, 2023
/s/ Charles Warden Charles Warden	Chairman of the Board	March 6, 2023
/s/ Jeffrey S. Heier, M.D. Jeffrey S. Heier, M.D.	Director	March 6, 2023
/s/ Seung Suh Hong, PH.D. Seung Suh Hong, PH.D.	Director	March 6, 2023
/s/ Richard L. Lindstrom, M.D. Richard L. Lindstrom, M.D.	Director	March 6, 2023
/s/ Merilee Raines Merilee Raines	Director	March 6, 2023
/s/ Leslie Williams Leslie Williams	Director	March 6, 2023

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OCULAR THERAPEUTIX, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Ocular Therapeutix, Inc.

Opinions on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ocular Therapeutix, Inc. and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations and comprehensive loss, of stockholders' equity (deficit) and of cash flows for each of the three years in the period ended December 31, 2022, including 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 as of 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 accounting principles generally accepted in the United States of America.

Emphasis of Matter

As discussed in Note 1 to the consolidated financial statements, the Company will require additional financing to fund future operations. Management's evaluation of the events and conditions and management's plans to mitigate these matters are also described in Note 1.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters 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.

Valuation of the Derivative Liability

As described in Notes 2, 10 and 11 to the consolidated financial statements, the Company's derivative liability balance was $6.4 million as of December 31, 2022 and the change in fair value recorded in other income (expense), net was $13.8 million for the year ended December 31, 2022. The derivative liability was recorded at fair value upon the

issuance of the 2026 convertible notes and is subsequently remeasured to fair value at each reporting period. The derivative liability was initially valued and remeasured using a "with-and-without" method. The "with-and-without" methodology involves valuing the whole instrument on an as-is basis and then valuing the instrument without the embedded conversion option. The difference between the entire instrument with the embedded conversion option compared to the instrument without the embedded conversion option is the fair value of the derivative, recorded as the derivative liability. The fair value of the 2026 convertible notes with and without the conversion option is estimated using a binomial lattice approach. The main inputs to valuing the 2026 convertible notes with the conversion option as of December 31, 2022 include the Company's stock price on the valuation date, the expected annual volatility of the Company's stock and the bond yield. The significant assumption used in determining the bond yield is the market yield movements of a comparable instrument issued as of the valuation date, which is assessed and updated each period.

The principal considerations for our determination that performing procedures relating to the valuation of the derivative liability is a critical audit matter are the significant judgment by management to determine the fair value of the derivative liability using a binomial lattice approach; this in turn led to a high degree of auditor judgment, subjectivity, and effort in performing procedures and in evaluating the audit evidence obtained related to the valuation of the derivative liability and management's significant assumption related to market yield movements used in determining the bond yield input. In addition, the audit effort involved the use of professionals with specialized skill and knowledge.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included, among others (i) the involvement of professionals with specialized skill and knowledge to assist in developing an independent range of fair values for the derivative liability and (ii) comparing the independent estimate to management's fair value estimate to evaluate the reasonableness of management's estimate. Developing the independent estimate involved testing the completeness and accuracy of the inputs provided by management and evaluating the reasonableness of management's significant assumption related to market yield movements used in determining the bond yield by considering observable data.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 6, 2023

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

OCULAR THERAPEUTIX, 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	$ 102,300	$ 164,164
Accounts receivable, net	21,325	21,135
Inventory	1,974	1,250
Prepaid expenses and other current assets	4,028	4,751
Total current assets	129,627	191,300
Property and equipment, net	9,856	6,956
Restricted cash	1,764	1,764
Operating lease assets	8,042	4,867
Total assets	$ 149,289	$ 204,887
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 5,123	$ 4,592
Accrued expenses and other current liabilities	24,097	20,121
Deferred revenue	576	—
Operating lease liabilities	1,599	1,624
Total current liabilities	31,395	26,337
Other liabilities:		
Operating lease liabilities, net of current portion	8,678	5,924
Derivative liability	6,351	20,192
Deferred revenue, net of current portion	13,387	13,000
Notes payable, net of discount	25,257	25,000
Other Non-Current Liabilities	93	—
2026 convertible notes, net	28,749	26,435
Total liabilities	113,910	116,888
Commitments and contingencies (Note 17)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized and no shares issued or outstanding at December 31, 2022 and December 31, 2021, respectively	—	—
Common stock, $0.0001 par value; 200,000,000 shares authorized and 77,201,819 and 76,731,940 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	8	8
Additional paid-in capital	652,213	633,795
Accumulated deficit	(616,842)	(545,804)
Total stockholders' equity	35,379	87,999
Total liabilities and stockholders' equity	$ 149,289	$ 204,887

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

OCULAR THERAPEUTIX, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except share and per share data)

	Year Ended December 31,		
	2022	2021	2020
Revenue:			
Product revenue, net	$ 50,457	$ 43,522	$ 17,403
Collaboration revenue	1,037	—	—
Total revenue, net	51,494	43,522	17,403
Costs and operating expenses:			
Cost of product revenue	4,540	4,406	2,083
Research and development	53,462	50,083	28,694
Selling and marketing	39,922	35,190	26,614
General and administrative	32,224	31,880	22,859
Total costs and operating expenses	130,148	121,559	80,250
Loss from operations	(78,654)	(78,037)	(62,847)
Other income (expense):			
Interest income	798	33	168
Interest expense	(7,022)	(6,671)	(6,768)
Change in fair value of derivative liability	13,841	78,121	(86,189)
Other income (expense), net	(1)	1	—
Total other (expense) income, net	7,616	71,484	(92,789)
Net loss	$ (71,038)	$ (6,553)	$ (155,636)
Net loss per share, basic	$ (0.92)	$ (0.09)	$ (2.56)
Weighted average common shares outstanding, basic	76,875,035	76,392,870	60,752,225
Net loss per share, diluted	$ (0.97)	$ (0.98)	$ (2.56)
Weighted average common shares outstanding, diluted	82,644,267	82,162,102	60,752,225

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

OCULAR THERAPEUTIX, INC.

CONSOLIDATED STATEMENTS OF CHANGES IN STOCKHOLDERS' EQUITY (DEFICIT)

(In thousands, except share data)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Par Value			
Balances at December 31, 2019	50,333,559	5	379,980	(383,615)	(3,630)
Issuance of common stock upon exercise of stock options	567,776	1	2,585	—	2,586
Issuance of common stock in connection with employee stock purchase plan	161,175	—	747	—	747
Issuance of common stock upon public offering, net of issuance costs	24,934,222	2	224,495	—	224,497
Stock-based compensation expense	—	—	7,531	—	7,531
Net loss	—	—	—	(155,636)	(155,636)
Balances at December 31, 2020	75,996,732	8	615,338	(539,251)	76,095
Issuance of common stock upon exercise of stock options	598,923	—	2,586	—	2,586
Issuance of common stock in connection with employee stock purchase plan	124,548	—	985	—	985
Issuance of common stock upon cashless exercise of warrant	11,737	—	—	—	—
Common stock issuance costs	—	—	(91)	—	(91)
Stock-based compensation expense	—	—	14,977	—	14,977
Net loss	—	—	—	(6,553)	(6,553)
Balances at December 31, 2021	76,731,940	8	633,795	(545,804)	87,999
Issuance of common stock upon exercise of stock options	137,502	—	514	—	514
Issuance of common stock in connection with employee stock purchase plan	332,377	—	940	—	940
Stock-based compensation expense	—	—	16,964	—	16,964
Net loss	—	—	—	(71,038)	(71,038)
Balances at December 31, 2022	77,201,819	$ 8	$ 652,213	$ (616,842)	$ 35,379

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

OCULAR THERAPEUTIX, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Year Ended December 31,		
	2022	2021	2020
Cash flows from operating activities:			
Net loss	$ (71,038)	$ (6,553)	$ (155,636)
Adjustments to reconcile net loss to net cash used in operating activities			
Stock-based compensation expense	16,964	14,977	7,531
Non-cash interest expense	4,853	4,628	4,415
Change in fair value of derivative liability	(13,841)	(78,121)	86,189
Depreciation and amortization expense	2,109	2,421	2,773
Gain (loss) on disposal of property and equipment	1	(1)	—
Changes in operating assets and liabilities:			
Accounts receivable	(190)	(8,883)	(9,704)
Prepaid expenses and other current assets	723	(101)	(2,419)
Inventory	(724)	(49)	(247)
Operating lease assets	(3,175)	977	811
Accounts payable	(621)	1,796	(452)
Accrued expenses	1,644	3,717	2,311
Deferred revenue	963	1,000	12,000
Operating lease liabilities	2,729	(1,358)	(1,125)
Net cash used in operating activities	(59,603)	(65,550)	(53,554)
Cash flows from investing activities:			
Purchases of property and equipment	(3,715)	(1,194)	(841)
Net cash used in investing activities	(3,715)	(1,194)	(841)
Cash flows from financing activities:			
Proceeds from issuance of notes payable, net	—	3,722	—
Proceeds from exercise of stock options	514	2,586	2,585
Proceeds from issuance of common stock pursuant to employee stock purchase plan	940	985	747
Proceeds from the Paycheck Protection Program Loan	—	—	3,201
Repayment of the Paycheck Protection Program Loan	—	—	(3,201)
Proceeds from issuance of common stock upon public offering, net of issuance costs	—	—	224,682
Issuance costs from the issuance of common stock upon public offering	—	(275)	—
Repayment of notes payable	—	(4,167)	—
Net cash provided by financing activities	1,454	2,851	228,014
Net decrease in cash, cash equivalents and restricted cash	(61,864)	(63,893)	173,620
Cash, cash equivalents and restricted cash at beginning of period	165,928	229,821	56,201
Cash, cash equivalents and restricted cash at end of period	$ 104,064	$ 165,928	$ 229,821
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 2,147	$ 1,932	$ 2,354
Supplemental disclosure of non-cash investing and financing activities:			
Additions to property and equipment included in accounts payable and accrued expenses	$ 1,384	$ 181	$ 91
Public offering costs included in accounts payable and accrued expenses at balance sheet dates	$ —	$ —	$ 184

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

OCULAR THERAPEUTIX, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

(Amounts in thousands, except share and per share data)

1. Nature of the Business and Basis of Presentation

Ocular Therapeutix, Inc. (the "Company") was incorporated on September 12, 2006 under the laws of the State of Delaware. The Company is a biopharmaceutical company focused on the formulation, development and commercialization of innovative therapies for diseases and conditions of the eye using its proprietary bioresorbable hydrogel-based formulation technology. The Company's mission is to build an ophthalmology-focused biopharmaceutical company that capitalizes on the gaps that the Company believes increasingly exist in the ophthalmology sector between single product companies and large, multi-product pharmaceutical companies.

The Company is subject to risks common to companies in the biotechnology industry including, but not limited to, new technological innovations, protection of proprietary technology, dependence on key personnel, compliance with government regulations, regulatory approval and compliance, reimbursement, uncertainty of market acceptance of products and the need to obtain additional financing. Recently approved products will require significant sales, marketing and distribution support up to and including upon their launch. Product candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval, prior to commercialization.

The Company is currently commercializing DEXTENZA® (dexamethasone insert) 0.4mg, an intracanalicular insert for the treatment of post-surgical ocular inflammation and pain and for the treatment of ocular itching associated with allergic conjunctivitis, in the United States. The Company suspended the production of ReSure® Sealant, an ophthalmic device designed to prevent wound leaks in corneal incisions following cataract surgery, as of the fourth quarter of 2021 in order to focus our manufacturing resources on DEXTENZA. Currently, ReSure Sealant is not commercially available in the United States, and we have received only limited revenues from ReSure Sealant to date. The Company's most advanced product candidates are in either Phase 1 or Phase 2 of clinical stage development. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's intellectual property will be obtained, that any products developed will obtain necessary government regulatory approval and adequate reimbursement or that any approved products will be commercially viable. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will generate significant revenue from product sales. The Company operates in an environment of rapidly changing technology and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees and consultants. The Company may not be able to generate significant revenue from sales of any product for several years, if at all. Accordingly, the Company will need to obtain additional capital to finance its operations.

The Company has incurred losses and negative cash flows from operations since its inception, and the Company expects to continue to generate operating losses and negative cash flows from operations in the foreseeable future. As of December 31, 2022, the Company had an accumulated deficit of $616,842. Based on its current operating plan which includes estimates of anticipated cash inflows from product sales and cash outflows from operating expenses, the Company believes that its existing cash and cash equivalents of $102,300 as of December 31, 2022 will enable it to fund its planned operating expenses, debt service obligations and capital expenditures at least through the next 12 months from the issuance date of these consolidated financial statements. The future viability of the Company beyond that point is dependent on its ability to generate cash flows from the sale of DEXTENZA and raise additional capital to finance its operations. The Company will need to finance its operations through public or private securities offerings, debt financings, collaborations, strategic alliances, licensing agreements, royalty agreements, or marketing and distribution agreements. Although the Company has been successful in raising capital in the past, there is no assurance that it will be successful in obtaining such additional financing on terms acceptable to the Company, if at all. If the Company is unable to obtain funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs for product candidates, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations.

2. Summary of Significant Accounting Policies

Basis of Presentation and Principles of Consolidation

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). The accompanying consolidated financial statements reflect the operations of the Company and its wholly-owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, and the reported amounts of revenues and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the measurement and recognition of reserves for variable consideration related to product sales, revenue recognition related to a collaboration agreement that contains multiple promises, the fair value of derivatives, stock-based compensation, and realizability of net deferred tax assets. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company's estimates.

Cash Equivalents

The Company considers all short-term, highly liquid investments with original maturities of ninety days or less at date of purchase to be cash equivalents. Cash equivalents, which primarily consist of investments in money market funds, are stated at fair value.

Revenue Recognition

The Company recognizes revenue in accordance with Accounting Standards Codification ("ASC") Topic 606 – *Revenue from Contracts with Customers* ("ASC 606"). Under ASC 606, an entity recognizes revenue when a customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to be entitled to in exchange for those goods or services.

To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer, (ii) identify the performance obligations in the contract, (iii) determine the transaction price, (iv) allocate the transaction price to the performance obligations in the contract, and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue

The Company sells DEXTENZA in the United States primarily to a limited number of specialty distributors ("SDs") under individually negotiated distribution agreements. These customers then subsequently resell DEXTENZA to physicians, clinics and certain medical centers or hospitals. The Company also sells DEXTENZA directly to a small population of ambulatory surgery centers, or ASCs, based on individually negotiated direct distribution agreements (the "Direct Customers"). In addition, the Company enters into arrangements with health care providers and payors that provide for government mandated or privately negotiated rebates and chargebacks with respect to the purchase of DEXTENZA.

The Company recognizes revenue on product sales when the customer obtains control of the Company's product, which occurs at a point in time (upon delivery to the customer). Product revenues are recorded net of applicable reserves for variable consideration, including discounts and allowances.

Transaction Price, including Variable Consideration— Revenues from product sales are recorded net of off-invoice discounts and reserves which are established for our estimate of variable consideration. Components of variable consideration include trade discounts and allowances, product returns, government chargebacks, discounts and rebates, and other incentives, such as voluntary patient assistance, and other fee-for-service amounts that are detailed within contracts between the Company and its customers. These reserves, as detailed below, are based on the amounts earned, or to be claimed on the related sales, and are classified as reductions of accounts receivable or a current liability. These estimates take into consideration a range of possible outcomes which are probability-weighted in accordance with the expected value method in ASC 606 for relevant factors such as current contractual and statutory requirements, specific known market events and trends, industry data, and forecasted customer buying and payment patterns. Overall, these reserves reflect the Company's best estimates of the amount of consideration to which it is entitled based on the terms of the respective underlying contracts.

The amount of variable consideration which is included in the transaction price may be constrained, and is included in the net sales price, only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized under the contract will not occur in a future period. Actual amounts of consideration ultimately received may differ from the Company's estimates. If actual results in the future vary from the Company's original estimates, the Company will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

Trade Discounts and Allowances—The Company compensates (through trade discounts and allowances) its customers for sales order management, data, and distribution services. However, the Company has determined such services received to date are not distinct from the Company's sale of products to the customer and, therefore, these payments have been recorded as a reduction of revenue within the statement of operations and comprehensive loss, as well as a reduction to accounts receivables, net on the consolidated balance sheets.

Product Returns— Consistent with industry practice, the Company generally offers customers a limited right of return for product that has been purchased from the Company based on the products expiration date. The Company estimates the amount of its product sales that may be returned by its customers and records this estimate as a reduction of revenue in the period the related product revenue is recognized, as well as within accrued expenses and other current liabilities, in the accompanying consolidated balance sheets. The Company currently estimates product return reserves using available industry data and its own sales information, including its visibility into the inventory remaining in the distribution channel.

Government Chargebacks— Chargebacks for fees and discounts to qualified government healthcare providers represent the estimated obligations resulting from contractual commitments to sell products to qualified U.S. Department of Veterans Affairs hospitals and entities that are subject to the U.S. federal government 340B Drug Discount Program entities at prices lower than the list prices charged to SDs and Direct Customers. Chargeback amounts are generally determined at the time of resale to the qualified government healthcare provider by SDs and Direct Customers, and the Company generally issues credits for such amounts within a few weeks of the Customer's notification to the Company of the resale. Allowance for chargebacks also consist of credits that the Company expects to issue for units that remain in the distribution channel inventories at each reporting period-end that the Company expects will be sold to qualified healthcare providers, and chargebacks that customers have claimed, but for which the Company has not yet issued a credit. These allowances are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue and accounts receivables, net.

Government Rebates— The Company is subject to discount obligations under state Medicaid programs and Medicare. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included in accrued expenses and other current liabilities on the consolidated balance sheets. For Medicare, the Company also estimates the number of patients in the prescription drug coverage gap for whom the Company will owe an additional liability under the Medicare Part D program. For Medicaid programs, the Company estimates the portion of sales attributed to Medicaid patients and records a liability for the rebates to be paid to the respective state Medicaid programs. The Company's liability for these rebates consists of invoices received for claims from prior quarters that have not been paid or for which an invoice has not yet been received, estimates of claims for the current quarter, and estimated future claims that will be made for product that has been recognized as revenue, but which remains in the distribution channel inventories at the end of each reporting period.

Purchaser/Provider Discounts and Rebates— The Company offers rebate payments for which ASCs, hospital out-patient departments and other prescribers qualify by meeting quarterly purchase volumes of DEXTENZA under the Company's volume-based rebate program. The Company calculates rebate payment amounts due under this program quarterly, based on actual qualifying purchases and applies a contractual discount rate. In the third quarter of 2022, the Company implemented a separate off-invoice discount ("OID") rebate program whereby end-users receive the discounted price immediately upon purchase, rather than having to wait until the end of the quarter for a rebate payment. The OID amounts are generally determined at the time of resale by SDs or direct sales to ASCs by the Company. The Company generally issues credits for such amounts within a few weeks of the SD's notification to the Company of the resale. The Company includes the OID on the invoice when it sells to an ASC directly. The calculation of the accrual for all rebates is based on an estimate of claims that the Company expects to receive associated with product that has been recognized as revenue but also remains in the distribution channel inventories at the end of each reporting period. The adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included as an accrued expenses and other current liabilities for volume-based rebates and as a reduction of accounts receivable for OID rebates.

Other Incentives— Other incentives which the Company offers include voluntary patient assistance programs, such as the co-pay assistance program, which are intended to provide financial assistance to qualified commercially-insured patients with prescription drug co-payments required by payors. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that the Company expects to receive associated with product that has been recognized as revenue, but remains in the distribution channel inventories at the end of each reporting period. The adjustments are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability which is included as an accrued expenses and other current liabilities on the consolidated balance sheets.

Collaboration Revenue

The Company evaluates contracts that contain multiple promises to determine which promises are distinct. Promises are considered to be distinct and therefore, accounted for as separate performance obligations, provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer and (ii) the promise to transfer the good or service to the customer is separately identifiable from other promises in the contract. In assessing whether a promise is distinct, the Company considers factors such as whether: (i) the Company provides a significant service of integrating goods and/or services with other goods and/or services promised in the contract; (ii) one or more of the goods and/or services significantly modifies or customizes, or are significantly modified or customized by one or more of the other goods and/or services promised in the contract; and (iii) the goods and/or services are highly interdependent or highly interrelated. Individual goods or services (or bundles of goods and/or services) that meet both criteria for being distinct are accounted for as separate performance obligations. Promises that are not distinct at contract inception are combined and accounted for as a single performance obligation. Options to acquire additional goods and/or services are evaluated to determine if such option provides a material right to the customer that it would not have received without entering into the contract. If so, the option is accounted for as a separate performance obligation. If not, the option is considered a marketing offer which would be accounted for as a separate contract upon the customer's election.

The Company considers the existence of any significant financing component within its arrangements based on whether a substantive business purposes exist to support the payment structure other than to provide a significant benefit of financing. The Company measures the transaction price based on the amount of consideration to which the Company expects to be entitled in exchange for transferring the promised goods and/or services to the customer. The Company utilizes either the expected value method or the most likely amount method to estimate the amount of variable consideration, depending on which method is expected to better predict the amount of consideration to which the Company will be entitled. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved. With respect to arrangements that include payments for a development or regulatory milestone payment, the Company evaluates whether the associated event is considered likely of achievement and estimates the amount to be included in the transaction price using the most likely amount method. Milestone payments that are not within the Company's control or the licensee, such as those dependent upon receipt of regulatory approval, are not considered to be likely of achievement until the triggering event occurs. At the end of each reporting period, the Company re-evaluates the probability of achievement of each milestone and any related constraint, and if necessary, adjust its estimate of the overall transaction price. Any such adjustments are recorded on a

cumulative catch-up basis, which would affect revenue and net loss in the period of adjustment. For arrangements that include sales-based royalties, including milestone payments based upon the achievement of a certain level of product sales, wherein the license is deemed to be the sole or predominant item to which the payments relate, the Company recognizes revenue upon the later of: (i) when the related sales occur or (ii) when the performance obligation to which some or all of the payment has been allocated has been satisfied (or partially satisfied). Consideration that would be received for optional goods and/or services is excluded from the transaction price at contract inception.

Accounts Receivable

Accounts receivable arise from product sales and are recognized at the amounts invoiced to customers, net of applicable reserves for variable consideration. The Company analyzes the actual payment history of its customers, the aging of receivables, current customer-specific developments and economic trends to estimate the reserve for current expected credit losses.

Inventory

The Company values its inventories at the lower of cost or estimated net realizable value. Costs, which include amounts related to direct labor, materials and manufacturing overhead, are determined using standard costs, which approximate average cost. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period, and it writes down any excess and obsolete inventories to their estimated realizable value in the period in which the impairment is first identified. Such impairment charges, should they occur, are recorded within cost of product revenue.

The Company capitalizes inventory costs associated with the Company's products after regulatory approval when, based on management's judgment, future commercialization is considered probable and the future economic benefit is expected to be realized. Inventory acquired prior to receipt of marketing approval of a product candidate is expensed as research and development expense as incurred. Inventory that can be used in either the production of clinical or commercial product is expensed as research and development expense when selected for use in a clinical manufacturing campaign. Inventory produced that will be used in promotional marketing campaigns is expensed to selling and marketing expense when it is selected for use in a marketing program.

Fair Value Measurements

Certain assets and liabilities are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.

- Level 2—Observable inputs (other than Level 1 quoted prices) such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.

- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

Derivative Instruments

The Company recognizes all derivative instruments as either assets or liabilities at fair value through profit or loss on the Company's consolidated balance sheet. Changes in the estimated fair value of derivative instruments are recognized in other income (expense), net in the consolidated statements of operations and comprehensive loss.

If the Company determines that a financial or non-financial contract, a 'host contract', includes implicit or explicit terms that affect the cash flows of the contract in a manner similar to a stand-alone derivative instrument, an 'embedded derivative', the Company analyzes whether to account for the embedded derivative separately. The Company accounts for an embedded derivative not separately from the host contract if it is clearly and closely related to the host contract or if the entire contract is measured at fair value through profit or loss. In other cases, the Company accounts for an embedded derivative separately.

The 2026 Convertible Notes, as discussed in Note 9, allow the holders to convert all or part of the outstanding principal of their 2026 Convertible Notes into shares of the Company's common stock provided that no conversion results in a holder beneficially owning more than 19.99% of the issued and outstanding common stock of the Company. The entire embedded conversion option is required to be separated from the 2026 Convertible Notes and accounted for as a freestanding derivative instrument subject to derivative accounting. The main input when determining the fair value of the 2026 Convertible Notes is the bond yield that pertains to the host instrument without the conversion option. The significant assumption used in determining the bond yield is the market yield movements of a comparable instrument issued as of the valuation date, which is assessed and updated each period. Therefore, the entire conversion option is bifurcated from the underlying debt instrument and accounted for and valued separately from the host instrument. The Company measures the value of the embedded conversion option at its estimated fair value and recognizes changes in the estimated fair value in other income (expense), net in the consolidated statements of operations and comprehensive loss during the period of change. The embedded conversion is recognized as a derivative liability in the Company's consolidated balance sheet.

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation. Depreciation expense is recognized using the straight-line method over a three- to five-year estimated useful life. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the related asset. Expenditures for repairs and maintenance of assets are charged to expense as incurred. Upon retirement or sale, the cost and related accumulated depreciation of assets disposed of are removed from the accounts and any resulting gain or loss is included in loss from operations.

Leases

The Company determines whether an arrangement is or contains a lease at inception. Operating leases are recognized on the consolidated balance sheets as operating lease assets, current portion of lease liabilities and long-term lease liabilities. Operating lease assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. Operating lease liabilities and their corresponding operating lease assets are recorded based on the present value of lease payments over the expected remaining lease term. The operating lease assets also include any lease payments made and adjustments for prepayments and lease incentives. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilized its incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term an amount equal to the lease payments in a similar economic environment. Lease terms may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. The Company reassesses the lease term and remeasures the lease liability if triggering events occur. Lease expense for lease payments is recognized on a straight-line basis over the lease term.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment and right-of-use assets. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset over its fair value, determined based on discounted cash flows. The Company has had no impairment triggers of long-lived assets.

Research and Development Costs

Research and development costs are expensed as incurred. Included in research and development expenses are salaries, stock-based compensation and benefits of employees and other operational costs related to the Company's research and development activities, including external costs of outside vendors engaged to conduct preclinical studies and clinical trials, manufacturing costs of the Company's products prior to regulatory approval, costs related to collaboration agreements and facility-related expenses.

The Company records accruals for estimated ongoing research and development costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies, including the phase or completion of events, invoices received and contracted costs. Judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Advertising Costs

Advertising costs are expensed as incurred.

Accounting for Stock-Based Compensation

The Company measures all stock options and other stock-based awards granted to employees, directors, and nonemployees at the fair value on the date of the grant. The fair value of the awards is recognized as expense, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award. The straight-line method of expense recognition is applied to all awards with service-only conditions.

The Company recognizes compensation expense for only the portion of awards that are expected to vest. In developing a forfeiture rate estimate, the Company has considered its historical experience to estimate pre-vesting forfeitures for service-based awards. The impact of a forfeiture rate adjustment will be recognized in full in the period of adjustment, and if the actual forfeiture rate is materially different from the Company's estimate, the Company may be required to record adjustments to stock-based compensation expense in future periods.

Compensation cost related to shares purchased through the Company's employee stock purchase plan, which is considered compensatory, is based on the estimated fair value of the shares on the offering date, including consideration of the discount and the look-back period. The Company estimates the fair value of the shares using a Black-Scholes option pricing model. Compensation expense is recognized over the six-month withholding period prior to the purchase date.

The Company classifies stock-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Income Taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred taxes are determined based on the difference between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect in the years in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the

tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate.

Interest and penalties related to income taxes are recorded as part of the income tax provision.

Segment Data

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's singular focus is on advancing its bioresorbable hydrogel product candidates for the programed-release delivery of therapeutic agents, specifically for ophthalmology. All property and equipment, net and all operating lease assets are held in the United States. All product revenue, net is attributable to the United States. Collaboration revenue is attributable to a customer in China (Note 3).

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. For the years ended December 31, 2022, 2021 and 2020, there were no items that gave rise to other comprehensive loss and therefore, there was no difference between net loss and comprehensive loss.

Net Loss Per Share

Basic net loss per share attributable to common stockholders is computed by dividing the net loss attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period. Diluted net loss attributable to common stockholders is computed by adjusting net loss attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities, outstanding stock options and common stock warrants, except where the result would be anti-dilutive. Diluted net loss per share attributable to common stockholders is computed by dividing the diluted net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of the conversion of convertible debt securities, the exercise of outstanding stock options and common stock warrants. In the diluted net loss per share calculation, net loss would also be adjusted for the elimination of interest expense on convertible debt securities and the mark-to-market gain or loss on bifurcated conversion options, if the impact was not anti-dilutive.

Recently Adopted Accounting Pronouncements

In August 2020, the FASB issued ASU No. 2020-06, Debt – Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40) ("ASU 2020-06"). This standard amends the guidance on convertible instruments and the derivatives scope exception for contracts in an entity's own equity and improves and amends the related earnings per share guidance for both Subtopics. The amendments in the ASU are effective for public business entities that meet the definition of an SEC filer, excluding entities eligible to be smaller reporting companies as defined by the SEC, for fiscal years beginning after December 15, 2021, including interim periods within those fiscal years. The Company adopted this accounting pronouncement as required effective January 1, 2022 and its adoption did not have a material impact on the consolidated financial statements.

Recently Issued Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB and adopted by us as of the specified effective date. The Company believes that recently issued accounting pronouncements that are not yet effective will not have a material impact on our consolidated financial statements and disclosures.

3. Licensing Agreements and Deferred Revenue

Incept License Agreement (in-licensing)

On September 13, 2018, the Company entered into a second amended and restated license agreement (the "Second Amended Agreement") with Incept, LLC ("Incept") to use and develop certain intellectual property (the "Incept License"). Under the Incept License, as amended and restated, the Company was granted a worldwide, perpetual, exclusive license to develop and commercialize products that are delivered to or around the human eye for diagnostic, therapeutic or prophylactic purposes relating to ophthalmic diseases or conditions. The Company is obligated to pay low single-digit royalties on net sales of commercial products developed using the licensed technology, commencing with the date of the first commercial sale of such products and until the expiration of the last to expire of the patents covered by the license. Any of the Company's sublicensees also will be obligated to pay Incept a royalty equal to a low single-digit percentage of net sales made by it and will be bound by the terms of the agreement to the same extent as the Company. The Company is obligated to reimburse Incept for its share of the reasonable fees and costs incurred by Incept in connection with the prosecution of the patent applications licensed to the Company under the Incept License.

Royalties paid under this agreement related to product sales were $1,466, $1,333 and $269 for the years ended December 31, 2022, 2021 and 2020, respectively. Royalties have been charged to cost of product revenue.

AffaMed License Agreement (out-licensing)

On October 29, 2020, the Company entered into license agreement ("License Agreement") with AffaMed Therapeutic Limited ("AffaMed") for the development and commercialization of the Company's DEXTENZA product regarding ocular inflammation and pain following cataract surgery and allergic conjunctivitis (collectively, the "DEXTENZA Field") and for the Company's OTX-TIC product candidate (collectively with DEXTENZA, the "AffaMed Licensed Products") regarding open-angle glaucoma or ocular hypertension (collectively, the "TIC Field" and, with the DEXTENZA Field, each a "Field"), in each case in mainland China, Taiwan, Hong Kong, Macau, South Korea, and the countries of the Association of Southeast Asian Nations (collectively, the "Territories"). The Company retains development and commercialization rights for the AffaMed Licensed Products in the rest of the world.

Under the License Agreement, the Company received a non-refundable upfront payment of $12,000 in December 2020, a $1,000 milestone in the fourth quarter of 2021 and a $2,000 clinical support payment in the second quarter of 2022. The Company is also eligible to receive up to an additional $88,000 in aggregate upon the achievement of certain regulatory, development and commercial milestones. The Company is also entitled to receive tiered, escalating royalties on the net sales of the AffaMed Licensed Products ranging from a low-teen to low-twenties percentage. Royalties under the License Agreement are payable on an AffaMed Licensed Product-by-AffaMed Licensed Product and jurisdiction-by-jurisdiction basis and are subject to potential reductions in specified circumstances, subject to a specified floor.

Under the License Agreement, the Company is generally responsible for expenses related to the development of the AffaMed Licensed Products in the applicable Fields in the Territories, provided that AffaMed (i) reimburse the Company a low-teen percentage of expenses incurred in connection with certain clinical trials conducted by the Company and designed to support marketing approval of the AffaMed Licensed Product by the FDA or the European Medicines Agency ("Global Studies"); (ii) is solely responsible for expenses incurred in connection with territory-specific clinical trials that it conducts in furtherance of the development plan agreed between the parties in the applicable Fields in the Territories ("Local Studies"); and (iii) reimburse the Company in full for expenses incurred in connection with obtaining and maintaining regulatory approvals of the AffaMed Licensed Products in the applicable Fields in the Territories. In the event AffaMed declines to participate in a Global Study or to conduct a Local Study in any jurisdiction in which the Company determines to conduct such a study, the Company is relieved of its obligation to provide AffaMed clinical data from such study, other than safety data, unless AffaMed subsequently reimburses the Company in the amounts described above plus a prespecified premium.

The License Agreement expires upon the expiration of the last royalty term for the last AffaMed Licensed Product in any applicable Field in the Territories. Either party may, subject to specified cure periods, terminate the License Agreement in the event of the other party's uncured breach. Either party may also terminate the License Agreement under specified circumstances relating to the other party's insolvency. AffaMed has the right to terminate the License Agreement at any time after completion of a Phase 3 clinical trial for OTX-TIC for any or no reason upon providing the Company three months' notice. During an established period following its change of control or its entry into a global

licensing agreement that includes the Territories with a third party, the Company has the option to terminate the License Agreement, subject to a specified notice period and the repayment of any costs and expenses incurred by AffaMed in connection with the License Agreement, including upfront and milestone payments AffaMed has previously paid to the Company, at a prespecified premium.

The Company concluded that AffaMed is a customer in this arrangement, and as such, the arrangement falls within the scope of the revenue recognition guidance in ASC 606.

At the inception of the License Agreement, the Company identified the following performance obligations in the agreement:

- the license, regulatory filings and manufacturing of DEXTENZA (the "DEXTENZA Field performance obligation");

- the license, regulatory filings and manufacturing for the Company's OTX-TIC product candidate regarding open-angle glaucoma or ocular hypertension in the Territories (the "OTX-TIC Field performance obligation");

- the conduct of a Phase 2 clinical trial of OTX-TIC (the "Phase 2 Clinical Trial of OTX-TIC performance obligation"); and

- obligations to participate on various joint research, development and project committees; the Company has concluded that this performance obligation is not material.

The transaction price was allocated to the performance obligations based on the relative estimated standalone selling prices of each performance obligation.

The Company developed the estimated standalone selling price for the services and/or manufacturing and supply included in each of the performance obligations, as applicable, primarily based on the nature of the services to be performed and/or goods to be manufactured and estimates of the associated costs, adjusted for a reasonable profit margin that would be expected to be realized under similar contracts.

The Company has determined that any sales-based royalties and milestones will be recognized as the Company delivers the clinical and commercial manufactured product to AffaMed. Any changes in estimates may result in a cumulative catch-up based on the number of units of manufactured product delivered.

As of December 31, 2022, the transaction price was determined to be $15,000. All potential regulatory, development and commercial milestone payments in the amount of $88,000 did not meet the recognition criteria under the most likely method, because their achievement was highly dependent on factors outside the control of the Company and therefore, were excluded from the transaction price as of December 31, 2022. Furthermore, under the expected value method the Company excluded the potential royalties from the transaction price.

We recognize revenue related to the amounts allocated to the DEXTENZA Field performance obligation and the OTX-TIC Field performance obligation based on the point in time upon which control of supply is transferred to AffaMed for each delivery of the associated supply. The Company currently expects to recognize the revenue over a period of approximately seven to eight years commencing on the date the Company begins delivering product to AffaMed. This estimate of this period considers the timing of development and commercial activities under the License Agreement and may be reduced or increased based on the various activities as directed by the joint committees, decisions made by AffaMed, regulatory feedback or other factors not currently known.

The Company recognized $1,037, $0 and $0 of collaboration revenue related to the Phase 2 Clinical Trial of OTX-TIC performance obligation for the years ended December 31, 2022, 2021 and 2020, respectively.

As of December 31, 2022, the aggregate amount of the transaction price allocated to the partially unsatisfied Phase 2 Clinical Trial of OTX-TIC performance obligation was $963. This amount is expected to be recognized as this performance obligation is satisfied through June 2025.

Deferred revenue activity for the year ended December 31, 2022 was as follows:

	Deferred Revenue
Deferred revenue at December 31, 2021	$ 13,000
Additions	2,000
Amounts recognized into revenue	(1,037)
Deferred revenue at December 31, 2022	$ 13,963

Regeneron Collaboration Agreement

On October 10, 2016, the Company entered into a Collaboration, Option and License Agreement (the "Regeneron Collaboration Agreement") with Regeneron Pharmaceuticals, Inc. ("Regeneron") for the development and potential commercialization of products using the Company's hydrogel in combination with Regeneron's large molecule VEGF-targeting compounds for the treatment of retinal diseases.

Under the terms of the Collaboration Agreement, the Company and Regeneron had agreed to conduct a joint research program with the aim of developing a sustained-release formulation of aflibercept, currently marketed under the tradename Eylea, that is suitable for advancement into clinical development. The Company had granted Regeneron an option (the "Option") to enter into an exclusive, worldwide license to develop and commercialize products using the Company's hydrogel in combination with Regeneron's large molecule VEGF-targeting compounds ("Licensed Products"). Under the term of the Collaboration Agreement, Regeneron was responsible for funding an initial preclinical tolerability study. The Regeneron Collaboration Agreement was subsequently amended on May 8, 2020 (the "Regeneron Amendment"). Pursuant to the Regeneron Amendment, the Company and Regeneron had adopted a new work plan to transition joint efforts under the Regeneron Collaboration Agreement to the research and development of an extended-delivery formulation of aflibercept to be delivered to the suprachoroidal space. Regeneron had agreed to pay personnel and material costs of the Company for specified preclinical development activities in connection with the revised work plan, as well as certain other costs. In addition, the Regeneron Amendment provided for the modification of the terms of the Option previously granted to Regeneron under the Regeneron Collaboration Agreement. As amended, the Option was exclusive for twenty-four months following May 8, 2020. On August 5, 2021, Regeneron notified the Company of its termination of the Regeneron Collaboration Agreement, as amended. The termination became effective immediately.

In connection with the termination of the Regeneron Collaboration Agreement, all licenses, options and other rights granted to either party under the Regeneron Collaboration Agreement automatically terminated, other than the surviving joint intellectual property rights described below. The Company and Regeneron also became obligated to undertake certain transition activities upon the termination, including the return of specified property of the other party. Each party retains an equal, undivided ownership interest, which may be transferred, licensed and otherwise exploited without a duty to account to the other party, in certain intellectual property rights jointly developed under the collaboration.

As a result of the termination, the Company is no longer eligible to receive (i) reimbursement from Regeneron for ongoing research and development activities, (ii) a fee upon exercise of the Option, (iii) payments upon the achievement of specified development and regulatory milestones of the Regeneron Licensed Products, or (iv) tiered, escalating royalties in a range from a high-single digit to a low-to-mid teen percentage of net sales of Regeneron Licensed Products, in each case pursuant to the Regeneron Collaboration Agreement. The Company is also no longer obligated to reimburse Regeneron for certain development costs, up to an aggregate amount of $30,000 in certain circumstances, were Regeneron to have exercised the Option.

For the years ended December 31, 2022, 2021 and 2020, the Company had recorded $0, $768 and $1,256 related to work performed for preclinical development activities in connection with the revised work plan which the Company has recorded as a reduction of research and development expense as this research is not an output of the Company's ordinary business activities. As of December 31, 2022 and 2021, the Company had not recorded any assets or liabilities with regard to the Regeneron Collaboration Agreement.

4. Cash Equivalents and Restricted Cash

The Company's statements of cash flows include restricted cash with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on such statements. A reconciliation of the cash, cash equivalents, and restricted cash reported within the balance sheet that sum to the total of the same amounts shown in the statement of cash flows is as follows:

	December 31, 2022	December 31, 2021	December 31, 2020
Cash and cash equivalents	$ 102,300	$ 164,164	$ 228,057
Restricted cash	1,764	1,764	1,764
Total cash, cash equivalents and restricted cash as shown on the statements of cash flows	$ 104,064	$ 165,928	$ 229,821

As of December 31, 2022, 2021 and 2020, the Company held restricted cash of $1,764, respectively, on its consolidated balance sheet. The Company held restricted cash as security deposits for its real estate leases.

5. Inventory

Inventory consisted of the following:

	December 31, 2022	December 31, 2021
Raw materials	$ 309	$ 388
Work-in-process	899	605
Finished goods	766	257
	$ 1,974	$ 1,250

6. Property and Equipment, net

Property and equipment, net consisted of the following:

	December 31, 2022	December 31, 2021
Equipment	$ 12,485	$ 10,989
Leasehold improvements	9,074	9,074
Furniture and fixtures	1,268	1,286
Software	236	236
Construction in progress	4,071	578
	27,134	22,163
Less: Accumulated depreciation and amortization	(17,278)	(15,207)
	$ 9,856	$ 6,956

Depreciation and amortization expense was $2,109, $2,421 and $2,773 for the years ended December 31, 2022, 2021 and 2020, respectively.

7. Leases

The Company leases real estate, including laboratory, manufacturing and office space. The Company's leases have remaining lease terms ranging from less than 1 year to approximately 4.5 years. Certain leases include one or more options to renew, exercised at the Company's sole discretion, with renewal terms that can extend the lease term from one year to six years. All of the Company's leases qualify as operating leases.

The lease for the Company's 20,445 square feet of manufacturing space located at 36 Crosby Drive in Bedford, Massachusetts commenced on June 30, 2018 and is scheduled to expire on July 31, 2023. On October 18, 2022, the

Company exercised its option to extend the lease agreement by an additional five-year term, resulting in a new expiration date of July 31, 2028. Under the terms of the existing lease, rent for the five-year extension period will be based on the current fair market rent for comparable space in the building and in other similar buildings in the same rental market as of August 1, 2023, the commencement date of the additional five-year term. We have estimated the prevailing market rental rates at the time when we exercised the renewal option, and have included these in our remeasurement of the operating lease asset and the lease liability. This has resulted in an increase of the Operating lease assets and Operating lease liabilities of $4,284 as of the remeasurement date. As this is an estimate for variable payments that depend on an index or a rate, we will not remeasure the payments for the five-year renewal period even if actual rent as of the commencement date of the five-year extension term, August 1, 2023, is different from our estimate.

The lease for approximately 70,712 square feet of general office, research and development and manufacturing space located at 15 Crosby Drive in Bedford, Massachusetts. The lease term commenced on February 1, 2017 and will expire on July 31, 2027. The Company has the option to extend the lease for two additional periods of five years each by delivering written notice of the exercise not earlier than fifteen months nor later than 12 months before expiration of the original term.

The lease for 30,036 square feet of office space located at 24 Crosby Drive in Bedford, Massachusetts commenced on April 18, 2019 and terminates on March 24, 2024 and does not include any lease renewal options.

Recognized lease costs were as follows:

	For the Year Ended December 31, 2022	For the Year Ended December 31, 2021	For the Year Ended December 31, 2020
Operating lease costs	$ 2,369	$ 2,482	$ 2,418
Variable lease costs	756	629	677
Total lease costs	$ 3,125	$ 3,111	$ 3,095

The minimum lease payments for the next five years and thereafter are expected to be as follows:

Year Ending December 31,	December 31, 2022
2023	2,663
2024	2,796
2025	2,674
2026	2,709
2027	2,111
Thereafter	716
Total lease payments	$ 13,669
Less: interest	3,392
Present value of operating lease liabilities	$ 10,277

The following table summarizes the weighted average remaining lease term and the weighted average incremental borrowing rate used to determine the operating lease liability:

	December 31, 2022	December 31, 2021
Weighted average remaining lease term in years	4.9	4.8
Weighted average discount rate	13.41 %	13.55 %

Supplemental disclosure of cash flow information related to the Company's operating leases included in cash flows provided by operating activities in its consolidated statements of cash flows is as follows:

	For the Year Ended December 31, 2022	For the Year Ended December 31, 2021	For the Year Ended December 31, 2020
Cash paid for amounts included in the measurement of lease liabilities	$ 2,549	$ 2,482	$ 2,418

8. Expenses

The Company recognized $1,166, $1,925, and $1,344 of advertising expenses for the years ended December 31, 2022, 2021 and 2020, respectively.

Accrued expenses consisted of the following:

	December 31, 2022	December 31, 2021
Accrued payroll and related expenses	$ 7,509	$ 6,597
Accrued rebates and programs	3,560	3,615
Accrued professional fees	1,228	1,227
Accrued research and development expenses	1,816	1,102
Accrued interest payable on 2026 convertible notes	8,756	6,475
Accrued other	1,228	1,105
	$ 24,097	$ 20,121

9. Financial Liabilities

Convertible Notes

On March 1, 2019, the Company issued $37,500 of convertible notes which accrue interest at an annual rate of 6% of their outstanding principal amount, which is payable, along with the principal amount at maturity, on March 1, 2026, unless earlier converted, repurchased or redeemed (the "2026 Convertible Notes"). The Company presents accrued interest in accrued current liabilities because the notes are currently convertible and the interest is payable in cash. The effective annual interest rate for the 2026 Convertible Notes was 14.8% through December 31, 2022.

The holders of the 2026 Convertible Notes may convert all or part of the outstanding principal amount of their 2026 Convertible Notes into shares of the Company's common stock, par value $0.0001 per share, prior to maturity and provided that no conversion results in a holder beneficially owning more than 19.99% of the issued and outstanding common stock of the Company. The conversion rate is initially 153.8462 shares of the Company's common stock per $1,000 principal amount of the 2026 Convertible Notes, which is equivalent to an initial conversion price of $6.50 per share. The conversion rate is subject to adjustment in customary circumstances such as stock splits or similar changes to the Company's capitalization.

Upon conversion by the holder, other than a conversion based on a Corporate Transactions as defined below, the Company has the right to select the settlement of the conversion in either shares of common stock, cash, or in a combination thereof. Upon any conversion of any 2026 Convertible Note, the Company is obligated to make a cash payment to the holder of such 2026 Convertible Note for any interest accrued but unpaid on the principal amount converted.

- If the Company elects to satisfy such conversion by shares of common stock, the Company shall deliver to the converting holder in respect of each $1,000 principal amount of 2026 Convertible Notes being converted a number of common shares equal to the conversion rate in effect on the conversion date;

- If the Company elects to satisfy such conversion by cash settlement, the Company shall pay to the converting holder in respect of each $1,000 principal amount of 2026 Convertible Notes being converted cash in an amount equal to the sum of the Daily Conversion Values (as defined below) for each of the twenty (20) consecutive trading days during a specified period. The "Daily Conversion Values" is defined as each of the 20 consecutive trading days during the specified period, 5.0% of the product of (a) the conversion rate on such trading day and (b) the "Daily VWAP" on such trading day. The Daily VWAP is defined as each of the 20 consecutive trading days during the applicable Observation Period, the per share volume-weighted average price as displayed under the heading "Bloomberg VWAP" on the Bloomberg page for the Company.

- If the Company elects to satisfy such conversion by combination, the Company shall pay or deliver, as the case may be, in respect of each $1,000 principal amount of 2026 Convertible Notes being converted, a settlement amount equal to the sum of the "Daily Settlement Amounts" (as defined below) for each of the twenty (20) consecutive trading days during the specified period. The "Daily Settlement Amount" is defined as, for each of the 20 consecutive trading days during the specified period: (a) cash in an amount equal to the lesser of (i) the Daily Measurement Value (as defined below) and (ii) the Daily Conversion Value on such Trading Day; and (b) if the Daily Conversion Value on such trading day exceeds the Daily Measurement Value, a number of Shares equal to (i) the difference between the Daily Conversion Value and the Daily Measurement Value, divided by (ii) the Daily VWAP for such Trading Day. The "Daily Measurement Value" is defined as the Specified Dollar Amount (as defined below), if any, divided by 20. The "Specified Dollar Amount" is defined as the maximum cash amount per $1,000 principal amount of Notes to be received upon conversion as specified in the notice specifying the Company's chosen settlement method.

In the event of a Corporate Transaction, the noteholder shall have the right to either (a) convert all of the unpaid principal at the conversion rate and receive a cash payment equal to (i) the outstanding accrued but unpaid interest under the 2026 Convertible Note to, but excluding, the corporate transaction conversion date (to the extent such date occurs prior to March 1, 2026, the maturity date of the 2026 Convertible Notes) plus (ii) and an additional amount of consideration based on a sliding scale depending on the date of such as Corporate transaction or (b) require the Company to repurchase all or part of the outstanding principal amount of such 2026 Convertible Note at a repurchase price equal to 100% of the outstanding principal amount of the 2026 Convertible Note to be repurchased, plus accrued and unpaid interest to, but excluding, the repurchase date.

A corporate transaction includes (i) a merger or consolidation executed through a tender offer or change of control (other than one in which stockholders of the Company own a majority by voting power of the outstanding shares of the surviving or acquiring corporation); (ii) a sale, lease, transfer, of all or substantially all of the assets of the Company; or (iii) if the Company's common stock ceases to be listed or quoted on any of the New York Stock Exchange, the Nasdaq Global Select Market, the Nasdaq Global Market or the Nasdaq Capital Market (the "Corporate Transaction").

If the last reported sale price of the common stock has been at least 130% of the conversion rate then in effect for 20 of the preceding 30 trading days (including the last trading day of such period), the Company is entitled, at its option, to redeem all or part of the outstanding principal amount of the 2026 Convertible Notes, on a pro rata basis, at an optional redemption price equal to 100% of the outstanding principal amount of the 2026 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the optional redemption date.

The 2026 Convertible Notes are subject to acceleration upon the occurrence of specified events of default, including a default or breach of certain contracts material to the Company and the delisting and deregistration of the Company's common stock.

The Company determined that the embedded conversion option is required to be separated from the 2026 Convertible Notes and accounted for as a freestanding derivative instrument subject to derivative accounting. The allocation of proceeds to the conversion option results in a discount on the 2026 Convertible Notes. The Company is amortizing the discount to interest expense over the term of the 2026 Convertible Notes using the effective interest method.

A summary of the 2026 Convertible Notes at December 31, 2022 and 2021 is as follows:

	December 31, 2022	December 31, 2021
2026 Convertible Notes	$ 37,500	$ 37,500
Less: unamortized discount	(8,751)	(11,065)
Total	$ 28,749	$ 26,435

Notes Payable

The Company entered into a credit and security agreement in 2014 (as amended to date, the "Credit Agreement") establishing the Company's credit facility (the "Credit Facility").

In December 2018, the Company's total indebtedness under the Credit Facility was increased to $25,000. The Company was required to make interest-only payments under the Credit Facility until December 2020. Commencing in January 2021, the Company was required to make 36 equal monthly installments of principal in the amount of $694, plus interest, through December 2023. Amounts borrowed under the Credit Facility were at LIBOR base rate, subject to 2.00% floor, plus 7.25%. Prior to the Fourth Amendment (as defined below), the effective interest rate was 9.25%.

In June 2021, the Company entered into a Fourth Amended and Restated Credit and Security Agreement (the "Fourth Amendment") to amend the terms of its debt with existing lenders for total indebtedness of $20,833 and borrowed an incremental $4,167, for a total of $25,000 (the "2021 Amended Credit Facility"). The Company is required to make interest-only payments under the 2021 Amended Credit Facility through April 2024. Commencing in May 2024, the Company is required to make 19 equal monthly installments of principal in the amount of $1,042, plus interest, then on the maturity date, November 30, 2025 the remaining balance of $5,208 plus the exit fee, as defined below. In the event the Company achieves certain milestones under the 2021 Amended Credit Facility, the Company has the right to extend through April 1, 2026 and make 5 equal monthly installments of principal in the amount of $1,042, plus interest. The Company has not assumed the achievement of these milestones for purposes of disclosures herein.

Amounts borrowed under the 2021 Amended Credit Facility are at LIBOR base rate, subject to 1.00% floor, plus 6.75%. The interest rate on the date of the amendment was 8.8%. In addition, a final payment (exit fee) equal to 3.5% of amounts drawn under the Amended Credit Facility, or $875 based on borrowings of $25,000, is due upon the maturity date of November 30, 2025. The Company is accruing the exit fee through November 30, 2025.

The Company accounted for the Fourth Amendment as a modification in accordance with the guidance in ASC 470-50, Debt. Amounts paid to the lenders were recorded as debt discount and a new effective interest rate was established. The effective annual interest rate of the outstanding debt under the Fourth Amendment is 8.8%.

There are no financial covenants associated with the Fourth Amendment. However, the Fourth Amendment does contain negative covenants restricting the Company's activities, including limitations on dispositions, mergers or acquisitions; encumbering its intellectual property; incurring indebtedness or liens; paying dividends; making certain investments; and engaging in certain other business transactions. As of December 31, 2022, the Company was not in violation of any of its covenants under the Fourth Amendment. The obligations under the Fourth Amendment are subject to acceleration upon the occurrence of specified events of default, including a material adverse change in the Company's business, operations or financial or other condition. The debt is collateralized by substantially all of the Company's assets, including its intellectual property.

In accordance with the Credit Agreement, in connection with the Company's desire to issue and sell the 2026 Convertible Notes, the Company amended the terms of its debt with existing lenders in February 2019. The amendment added to the Credit Agreement, among other provisions, a negative covenant restricting the Company from paying the holders of the 2026 Convertible Notes ahead in priority to the existing lenders, for so long as indebtedness remains outstanding under the Credit Facility, and a cross-default provision to establish that an event of default under the purchase agreement for the 2026 Convertible Notes also constitutes an event of default under the Credit Agreement.

The Company has a total borrowing capacity of $25,000 under the 2021 Amended Credit Facility, which was fully drawn down as of December 31, 2022.

Borrowings outstanding are as follows:

	December 31, 2022	December 31, 2021
Borrowings outstanding	$ 25,000	$ 25,000
Accrued exit fee	335	110
Unamortized discount	(78)	(110)
Long-term notes payable	$ 25,257	$ 25,000

As of December 31, 2022, the annual repayment requirements for the Credit Facility, inclusive of the final payment of $875 due at expiration, were as follows:

Year Ending December 31,	Principal	Final Payment	Total
2023	—	—	—
2024	8,333	—	8,333
2025	16,667	875	17,542
	$ 25,000	$ 875	$ 25,875

10. Derivatives

Derivative Liability

The 2026 Convertible Notes (Note 9) contain an embedded conversion option that meets the criteria to be bifurcated and accounted for separately from the 2026 Convertible Notes (the "Derivative Liability"). The Derivative Liability was recorded at fair value upon the issuance of the 2026 Convertible Notes and is subsequently remeasured to fair value at each reporting period. The 2026 Convertible Notes, including the Derivative Liability, were initially valued and are remeasured using a "with-and-without" method. The "with-and-without" methodology involves valuing the whole instrument on an as-is basis and then valuing the 2026 Convertible Notes without the embedded conversion option. The difference between the entire instrument with the embedded conversion option compared to the instrument without the embedded conversion option is the fair value of the derivative, recorded as the Derivative Liability. Refer to Note 11 for details regarding the determination of fair value.

A roll forward of the derivative liability is as follows:

	As of
Balance at December 31, 2020	$ 98,313
Change in fair value	(78,121)
Balance at December 31, 2021	$ 20,192
Change in fair value	(13,841)
Balance at December 31, 2022	$ 6,351

Warrants

In April 2014, the Company entered into a credit facility with Silicon Valley Bank and MidCap Financial SBIC, LP, and it issued the lenders warrants to purchase 100,000 shares of its Series D-1 redeemable convertible preferred stock with an exercise price of $3.00 per share. Upon the closing of the Company’s IPO in July 2014, the preferred stock warrants became warrants to purchase an aggregate of 37,878 shares of its common stock with an exercise price of $7.92 per share, with Silicon Valley Bank and MidCap Financial SBIC, LP., each holding warrants of 18,939 shares of common stock.

The Company had warrants for the purchase of 18,939 shares of common stock outstanding with MidCap Financial SBIC, LP at December 31, 2020 at a weighted average exercise price of $7.92 per share and an expiration date of April 17, 2021. On January 29, 2021, holders of warrants to purchase 18,939 shares of common stock at an exercise price of $7.92 exercised their right to purchase their warrants. The exercise price of the warrants was paid through a net

share settlement mechanism and as a result the Company issued 11,737 shares of common stock to satisfy the exercise of all the warrants.

There are no warrants outstanding as of December 31, 2022 and 2021, respectively.

11. Risks and Fair Value

Concentration of Credit Risk and of Significant Suppliers and Customers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and cash equivalents and accounts receivable. The Company has all cash and cash equivalents balances at one accredited financial institution, in amounts that exceed federally insured limits. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on a small number of third-party manufacturers to supply products for research and development activities in its preclinical and clinical programs and for sales of its products. The Company's development programs as well as revenue from future sales of its product sales could be adversely affected by a significant interruption in the supply of any of the components of these products.

For the year ended December 31, 2022, three specialty distributor customers accounted for 44%, 25% and 17% of the Company's total revenue, and at December 31, 2022, three specialty distributor customers accounted for 52%, 24% and 15% of the Company's total accounts receivable. No other customer accounted for more than 10% of total revenue for the year ended December 31, 2022, or accounts receivable at December 31, 2022.

For the year ended December 31, 2021, three specialty distributor customers accounted for 42%, 26% and 17% of the Company's total revenue, and at December 31, 2021 and three specialty distributor customers accounted for 42%, 26% and 21% of the Company's total accounts receivable. No other customer accounted for more than 10% of total revenue for the year ended December 31, 2022, or accounts receivable at December 31, 2021.

For the year ended December 31, 2020, three specialty distributor customers accounted for 42%, 29% and 12% of the Company's total revenue.

Fair Value of Financial Assets and Liabilities

The following tables present information about the Company's financial assets and liabilities that are measured at fair value on a recurring basis as of December 31, 2022 and 2021 and indicate the level of the fair value hierarchy utilized to determine such fair value:

	Fair Value Measurements as of December 31, 2022 Using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 30,188	$ —	$ —	$ 30,188
Liability:				
Derivative liability (Note 10)	$ —	$ —	$ 6,351	$ 6,351

	Fair Value Measurements as of December 31, 2021 Using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 62,392	$ —	$ —	$ 62,392
Liability:				
Derivative liability (Note 10)	$ —	$ —	$ 20,192	$ 20,192

During the year ended December 31, 2022 and 2021, there were no transfers between Level 1 and 2.

The carrying value of accounts receivable, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair value due to the short-term nature of these assets and liabilities. The carrying value of the Company's variable interest rate notes payable are recorded at amortized costs, which approximates fair value due to the variable interest rate.

At December 31, 2022, the 2026 Convertible Notes, net of the Derivative Liability, were carried at amortized cost totaling $37,505, comprised of the $28,749 non-current liability (Note 9) and $8,756 accrued interest (Note 8). At December 31, 2021, the 2026 Convertible Notes, net of the Derivative Liability, were carried at amortized cost totaling $32,910, comprised of the $26,435 non-current liability (Note 9) and $6,475 accrued interest (Note 8). The estimated fair value of the 2026 Convertible Notes, without the Derivative Liability, was $33,177 and $32,598 at December 31, 2022 and 2021, respectively.

The fair value of the 2026 Convertible Notes with and without the conversion option is estimated using a binomial lattice approach. The use of this approach requires the use of Level 3 unobservable inputs. The main input when determining the fair value of the 2026 Convertible Notes is the bond yield that pertains to the host instrument without the conversion option. The significant assumption used in determining the bond yield is the market yield movements of a comparable instrument issued as of the valuation date, which is assessed and updated each period. The main input when determining the fair value for disclosure purposes is the bond yield which is updated each period to reflect the yield of a comparable instrument issued as of the valuation date. The estimated fair value presented is not necessarily indicative of an amount that could be realized in a current market exchange. The use of alternative inputs and estimation methodologies could have a material effect on these estimates of fair value.

The main inputs to valuing the 2026 Convertible Notes with the conversion option are as follows:

	As of	
	December 31, 2022	December 31, 2021
Company's stock price	$ 2.81	$ 6.97
Volatility	93.8 %	82.6 %
Bond yield	16.2 %	12.6 %

The bond yield was derived by making the fair value of the 2026 Convertible Notes equal to the face value on the issuance date. Fair value measurements are highly sensitive to changes in these inputs and significant changes in these inputs would result in a significantly higher or lower fair value.

12. Equity

Preferred Stock

The Amended and Restated Certificate of Incorporation authorized 5,000,000 shares of preferred stock, $0.0001 par value, all of which is undesignated and none of which are issued or outstanding at December 31, 2022 and 2021.

Common Stock

The Amended and Restated Certificate of Incorporation authorized 100,000,000 shares of the Company's common stock. Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. In June 2021, the Company adopted an amended and restated certificate of incorporation increasing the number of its authorized shares of its common stock to 200,000,000 shares.

On April 5, 2019, the Company entered into an Open Market Sales Agreement (the "2019 Sales Agreement") with Jefferies, under which the Company may offer and sell its common stock having aggregate proceeds of up to $50,000 from time-to-time through Jefferies, acting as agent. In the twelve months ended December 31, 2020, the Company sold 2,984,381 shares of common stock under the 2019 Sales Agreement, resulting in net proceeds of approximately

$14,359, respectively, after commissions and expenses. From inception through March 1, 2021, the Company sold an aggregate of 10,321,840 shares of common stock under the 2019 Sales Agreement, resulting in net proceeds of approximately $46,985 after commissions and expenses. On August 9, 2021, the Company and Jefferies mutually terminated the 2019 Sales Agreement and entered into another Open Market Sale Agreement (the "2021 Sales Agreement") under which the Company may offer and sell shares of common stock of the Company having an aggregate offering price of up to $100,000 from time to time through Jefferies, acting as agent. As of March 3, 2023, the Company has not sold any shares of common stock under the 2021 Sales Agreement.

On December 14, 2020, the Company entered into an underwriting agreement with Jefferies LLC ("Jefferies") and Piper Sandler & Co. (collectively with Jefferies, "the Underwriters") in connection with an underwritten public offering of 3,725,000 shares of the Company's common stock. Under the terms of this underwriting agreement, the Company also granted the Underwriters an option to purchase up to an additional 558,750 shares of common stock at the public offering price, less the underwriting discounts and commissions. The Underwriters subsequently exercised this option to purchase such option shares in full. The public offering price of the shares in this offering was $21.50 per share, and the Underwriters purchased all of the shares from the Company at a price of $20.21 per share. After deducting underwriting discounts and commissions and offering expenses, the Company received net proceeds from the offering of $86,390.

On October 13, 2020, the Company entered into an underwriting agreement with the Underwriters, in connection with an underwritten public offering of 7,180,000 shares of the Company's common stock. Under the terms of this underwriting agreement, the Company also granted the Underwriters an option to purchase up to an additional 1,077,000 shares of common stock at the public offering price, less the underwriting discounts and commissions. The Underwriters subsequently exercised this option to purchase such option shares in full. The public offering price of the shares in this offering was $9.75 per share, and the Underwriters purchased all of the shares from the Company at a price of $9.17 per share. After deducting underwriting discounts and commissions and offering expenses, the Company received net proceeds from the offering of $75,406.

In May 2020, the Company entered into an underwriting agreement with the Underwriters, in connection with an underwritten public offering of 8,181,819 shares of the Company's common stock. Under the terms of this underwriting agreement, the Company also granted the Underwriters an option to purchase up to an additional 1,227,272 shares of common stock at the public offering price, less the underwriting discounts and commissions. The Underwriters subsequently exercised this option to purchase such option shares in full. The public offering price of the shares in this offering was $5.50 per share, and the Underwriters purchased all of the shares from the Company at a price of $5.17 per share. After deducting underwriting discounts and commissions and offering expenses, the Company received net proceeds from the offering of $48,327.

As of December 31, 2022, the Company had reserved 21,653,015 shares of common stock for the exercise of outstanding stock options, the vesting of restricted stock units, and the number of shares remaining available for grant under the Company's 2021 Stock Incentive Plan, 2014 Stock Incentive Plan, the 2019 Inducement Stock Incentive Plan, and the 2014 Employee Stock Purchase Plan (Note 13).

13. Stock-Based Awards

For the years ended December 31, 2022 and 2021, the Company had four stock-based compensation plans under which it was able to grant stock-based awards, the 2014 Stock Incentive Plan (the "2014 Plan"), the 2021 Stock Incentive Plan (the "2021 Plan"), the 2019 Inducement Plan, and the 2014 Employee Stock Purchase Plan (the "ESPP"), collectively the "Stock Plans". Certain inducement awards made prior to inception of the 2019 Inducement Plan were issued outside of the Stock Plans. The purpose of the Stock Plans is to provide incentives to employees, directors, and nonemployee consultants. The 2014 Plan and the 2021 Plan provide for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock units ("RSUs"), stock appreciation rights and other stock-based awards. As of December 31, 2022 and 2021, respectively, the Company had an immaterial number of vested stock awards outstanding that were granted under the Company's 2006 Stock Incentive Plan (the "2006 Plan"). Effective as of the adoption of the 2014 Plan by the Company's stockholders in 2014, no new awards have been granted under the 2006 Plan. As of December 31, 2022, all then outstanding awards under the 2006 Plan remained in effect and continued to be governed by the terms of the 2006 Plan.

2014 Plan - The number of shares initially reserved for issuance under the 2014 Plan was 1,336,907 shares of common stock. Between 2014 and 2021, the number of shares reserved for issuance under the 2014 Plan increased to

8,622,647 as of January 1, 2021. On June 18, 2021, the Company's stockholders approved the adoption of the 2021 Plan previously approved by the board of directors. Effective as of the adoption of the 2021 Plan by the Company's stockholders, no new awards have been granted under the 2014 Plan. However, as of December 31, 2022, all then-outstanding awards under the 2014 Plan remained in effect and continued to be governed by the terms of the 2014 Plan.

2021 Plan - The number of shares initially reserved for issuance under the 2021 Plan was 6,000,000 shares of common stock; plus 456,334 shares remaining available for grant under the 2014 Plan as of immediately prior to the effective date of the 2021 Plan and 9,766,336 shares subject to awards granted under the 2014 Plan or the 2006 Plan, which awards expire, terminate or are otherwise surrendered, canceled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right (subject to certain limitations). On June 16, 2022, the Company's stockholders approved an increase of the number of shares of common stock that is reserved for issuance by 3,600,000. As of December 31, 2022, 5,863,174 shares remained available for issuance under the 2021 Plan.

2019 Inducement Plan - The 2019 Inducement Plan provides for the following types of awards, each of which is referred to as an "Award": non-statutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards. Awards under the 2019 Inducement Plan may only be granted to persons who (a) were not previously an employee or director of the Company or (b) are commencing employment with the Company following a bona fide period of non-employment, in either case as an inducement material to the individual's entering into employment with the Company and in accordance with the requirements of Nasdaq Stock Market Rule 5635(c)(4). For the avoidance of doubt, neither consultants nor advisors shall be eligible to participate in the 2019 Inducement Plan. Each person who is granted an Award under the 2019 Inducement Plan is deemed a "Participant". On December 10, 2020, the board of directors of the Company amended the 2019 Inducement Plan to increase the aggregate number of shares issuable by 554,000 shares of common stock to 1,054,000. As of December 31, 2022, 545,375 shares remained available for issuance under the 2019 Inducement Plan.

ESPP – The number of shares initially reserved for issuance under the ESPP was 207,402 shares of common stock. The number of shares of common stock that may be issued under the ESPP will automatically increase on the first day of each fiscal year, commencing on January 1, 2015 and ending on December 31, 2024, in an amount equal to the least of 207,402 shares of the Company's common stock, 0.5% of the number of shares of the Company's common stock outstanding on the first day of the applicable fiscal year, and an amount determined by the Company's board of directors. On January 1, 2022, the number of shares available for issuance under the ESPP increased by 207,402. As of December 31, 2022, 482,073 shares of common stock remained available for issuance.

Stock options granted pursuant to the Stock Plans, excluding awards under the ESPP, are granted at exercise prices not to be less than the fair value of common shares as of the date of grant. They generally require a service period of 4 years and generally vest monthly, or 1/4 on the first anniversary of the grant date, with the remainder vesting monthly over the remaining three years. Stock Options granted under the 2019 Inducement Plan may in addition be subject to performance-based vesting. The maximum contractual term of Stock Options granted under the Stock Plans is generally 10 years. RSUs granted pursuant to the Stock Plans generally require a service period of 3 years and generally vest 1/3 on each anniversary of the grant date.

Valuation of Awards

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option-pricing model. The expected life of the options was calculated using the simplified method. The simplified method defines the life as the average of the contractual term of the options and the weighted-average vesting period for all option tranches. The Company utilizes the simplified method because the Company does not have sufficient historical exercise data over the life of awards to provide a reasonable basis upon which to estimate expected term. The expected term of stock options granted to nonemployees is equal to the contractual term of the option award. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future. The Company uses its historical volatility to estimate expected volatility.

The assumptions that the Company used to determine the fair value of the stock options granted to employees and directors are as follows, presented on a weighted average basis:

	Year Ended December 31,		
	2022	2021	2020
Risk-free interest rate	2.10 %	0.80 %	1.12 %
Expected term (in years)	6	6	6
Expected volatility	81.14 %	87.65 %	86.00 %
Expected dividend yield	— %	— %	— %

For RSUs, the grant date fair value is the closing price of the Company's stock on the grant date.

Stock Options

The following table summarizes the Company's stock option activity:

	Shares Issuable Under Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (In years)	Aggregate Intrinsic Value
Outstanding as of December 31, 2021	10,934,828	$ 9.60	7.1	$ 13,283
Granted	3,834,053	4.95		
Exercised	(137,502)	3.69		
Cancelled/forfeited	(961,668)	8.45		
Outstanding as of December 31, 2022	13,669,711	$ 8.45	7.0	$ 7
Options vested and expected to vest as of December 31, 2022	12,179,808	$ 8.14	6.8	$ 7
Options exercisable as of December 31, 2022	8,565,338	$ 8.54	6.0	$ 7

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised was $186, $6,779 and $4,307 during the years ended December 31, 2022, 2021 and 2020, respectively.

The weighted average grant date fair value of stock options granted to employees and directors during the years ended December 31, 2022, 2021 and 2020 was $4.95, $12.48 and $5.93 per share, respectively.

As of December 31, 2022, there were 563,880 outstanding unvested service-based stock options held by nonemployees.

RSUs

The following table summarizes the Company's activity of unvested RSUs:

	RSU's	Weighted average grant date fair value
Unvested balance at December 31, 2021	—	$ —
Granted	1,173,898	5.04
Cancelled/forfeited	(81,216)	5.14
Unvested balance at December 31, 2022	1,092,682	$ 5.03

Each RSU is equivalent to one share of common stock upon vesting. Each RSU award vests on an annual basis over a three-year period. Holders of RSUs are not entitled to vote on any matters and are not entitled to dividends. The Company has determined the fair value of each RSU based on the closing price of the Company's common stock on the date of grant and recognizes the compensation expense using the straight-line method over the service period, which coincides with the vesting period.

Stock-based Compensation

The Company recorded stock-based compensation expense in the following expense categories of its statements of operations and comprehensive loss:

	Year Ended December 31,		
	2022	2021	2020
Research and development	$ 4,166	$ 3,750	$ 1,514
Selling and marketing	4,684	4,014	1,719
General and administrative	8,114	7,214	4,298
	$ 16,964	$ 14,978	$ 7,531

As of December 31, 2022, the Company had an aggregate of $20,620 of unrecognized stock-based compensation cost, which is expected to be recognized over a weighted average period of 2.4 years.

14. Employee Benefits

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan"). The 401(k) Plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. Company contributions to the plan may be made at the discretion of the board of directors. For the years ended December 31, 2022, 2021 and 2020, the Company has made contributions of $593, $493, and $0, respectively, to the 401(k) Plan.

15. Income Taxes

During the years ended December 31, 2022, 2021 and 2020, the Company recorded no income tax benefits for the net operating losses incurred or the research and development tax credits generated in each year, due to its uncertainty of realizing a benefit from those items.

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,		
	2022	2021	2020
Federal statutory income tax rate	21.0 %	21.0 %	21.0 %
Research and development tax credits	5.4	35.9	1.0
State taxes, net of federal benefit	2.6	19.3	1.0
Stock-based compensation	(2.1)	(7.8)	—
Derivative liability	2.7	244.7	(11.5)
Change in tax rate	1.4	(8.4)	—
Other	(0.1)	(3.8)	—
Change in the valuation allowance	(30.9)	(300.9)	(11.5)
Effective income tax rate	— %	— %	— %

Changes in the valuation of the derivative liability do not provide a future tax benefit. To the extent the deferred tax asset related to the derivative liability exceeds the deferred tax liability related to the 2026 Convertible Notes, the excess is recorded as a permanent item.

Net deferred tax assets consisted of the following:

	December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 113,801	$ 106,265
Tax credit carryforwards	19,653	15,853
Capitalized start-up costs	255	373
Capitalized research and development expenses, net - Sec. 59(e)	5,773	7,828
Capitalized research and development expenses, net Sec. 174	10,046	—
Operating lease liabilities	2,422	1,705
Derivative liability	1,497	2,499
Accrued expenses and other	15,057	11,712
Total deferred tax assets	168,504	146,235
Valuation allowance	(164,546)	(142,637)
Net deferred tax assets	3,958	3,598
Deferred tax liabilities:		
Operating lease right of use assets	(1,895)	(1,099)
2026 Convertible Notes	(2,063)	(2,499)
Total deferred tax liabilities	(3,958)	(3,598)
Net deferred tax assets	$ 0	$ —

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2022, 2021 and 2020 related primarily to the increase in net operating loss carryforwards, amortization of capitalized research and development expenses, and increase in research and development tax credit carryforwards were as follows:

	Year Ended December 31,		
	2022	2021	2020
Valuation allowance as of beginning of year	$ 142,637	$ 123,020	$ 105,062
Increases recorded to income tax provision	21,909	19,617	17,958
Valuation allowance as of end of year	$ 164,546	$ 142,637	$ 123,020

As of December 31, 2022, the Company had net operating loss ("NOL") carryforwards for federal and state income tax purposes of $453,276 and $322,110, respectively. The federal and state NOLs generated for annual periods prior to January 1, 2018 begin to expire in 2026. The Company's federal NOLs generated for the years ended since December 31, 2018, which amounted to a total of $327,471, can be carried forward indefinitely. As of December 31, 2022, the Company also had available research and development tax credit carryforwards for federal and state income tax purposes of $13,408 and $7,804, respectively, which begin to expire in 2026 and 2025, respectively. Utilization of the NOL carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986 ("Section 382") due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain shareholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since inception, utilization of the NOL carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments, as required. Any limitation may result in expiration of a portion of the NOL carryforwards or research and development tax credit carryforwards before utilization. Further, until a study is completed and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. Management considered the Company's cumulative net losses and concluded that it is more likely than not that

the Company would not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance was established against the net deferred tax assets as of December 31, 2022, 2021 and 2020.

The Company has not recorded any amounts for unrecognized tax benefits as of December 31, 2022, 2021 or 2020.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending income tax examinations. The Company's tax years are still open under statute from the Company's fiscal year 2019 to the present. Earlier years may be examined to the extent that tax credit or net operating loss carryforwards are used in future periods.

16. Net Loss Per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows for the years ended December 31, 2022, 2021 and 2020:

	2022	2021	2020
Numerator:			
Net loss attributable to common stockholders	$ (71,038)	$ (6,553)	$ (155,636)
Denominator:			
Weighted average common shares outstanding, basic	76,875,035	76,392,870	60,752,225
Net loss per share - basic	$ (0.92)	$ (0.09)	$ (2.56)

For the year ended December 31, 2020, there is no dilutive impact. Therefore, diluted net loss per share is the same as basic net loss per share. Basic and diluted net loss per share was calculated as follows for the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
Net loss attributable to common stockholders, basic	$ (71,038)	$ (6,553)
Interest expense on 2026 Convertible Notes	4,596	4,409
Change in fair value of derivative liability	(13,841)	(78,121)
Net loss attributable to common stockholders, diluted	$ (80,283)	$ (80,265)
Weighted average common shares outstanding, basic	76,875,035	76,392,870
Dilutive options (treasury stock method)	—	—
Shares issuable upon conversion of 2026 Convertible Notes, as if converted	5,769,232	5,769,232
Weighted average common shares outstanding, diluted	82,644,267	82,162,102
Net loss per share attributable to common stockholders, diluted	$ (0.97)	$ (0.98)

The Company excluded the following common stock equivalents, outstanding as of December 31, 2022, 2021 and 2020 from the computation of diluted net loss per share attributable to common stockholders for the years ended December 31, 2022, 2021 and 2020 because they had an anti-dilutive impact due to the net loss incurred for the periods.

The Company also excluded the shares issuable upon conversion of the 2026 Convertible Notes from the computation of diluted net loss per share for the year ended December 31, 2020 because they had an anti-dilutive impact.

	December 31,		
	2022	2021	2020
Options to purchase common stock	13,669,711	10,934,828	9,114,735
Restricted stock units	1,092,682	—	—
Shares issuable upon conversion of 2026 Convertible Notes, if converted	—	—	5,769,232
Warrants for the purchase of common stock	—	—	18,939
	14,762,393	10,934,828	14,902,906

17. Commitments and Contingencies

Indemnification Agreements

In the ordinary course of business, the Company enters into agreements that may include indemnification provisions. Pursuant to such agreements, the Company may indemnify, hold harmless and defend indemnified parties for losses suffered or incurred by the indemnified party. Some of the provisions will limit losses to those arising from third-party actions. In some cases, the indemnification will continue after the termination of the agreement. The maximum potential amount of future payments the Company could be required to make under these provisions is not determinable. To date, the Company has not incurred any material costs as a result of such indemnifications.

18. Related Party Transactions

In November 2020, the Company engaged Specialty Pharma Consulting, LLC (“Specialty Pharma”), an entity affiliated with Kevin Coughenour, to provide services for quality engineering and validation activities in the ordinary course of business. Mr. Coughenour is married to the Company’s former Chief Operating Officer Patricia Kitchen. On April 26, 2021, the Company and Specialty Pharma terminated their relationship. The Company incurred fees for quality engineering and validation activities rendered by Specialty Pharma of $0, $155 and $47 for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022 and 2021, there were no liabilities recorded with regard to Specialty Pharma.

The Company has engaged Wilmer Cutler Pickering Hale and Dorr LLP (“WilmerHale”) to provide certain legal services to the Company. The Company's Chief Business Officer’s sister is a managing partner at WilmerHale, who has not participated in providing legal services to the Company. The Company incurred fees for legal services rendered by WilmerHale of approximately $959, $1,396 and $1,772 for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022 and 2021, there was $0 and $119 recorded in accounts payable for WilmerHale. As of December 31, 2022 and 2021, there was $24 and $68 recorded in accrued expenses for WilmerHale.

19. Subsequent Events

The number of shares of common stock that may be issued under the ESPP will automatically increase on the first day of each fiscal year, commencing on January 1, 2015 and ending on December 31, 2024, in an amount equal to the least of 207,402 shares of the Company’s common stock, 0.5% of the number of shares of the Company’s common stock outstanding on the first day of the applicable fiscal year, and an amount determined by the Company’s board of directors. On January 1, 2023, the number of shares available for issuance under the ESPP increased by 207,402.

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ANNUAL MEETING

JUNE 14, 2023 - 8:30 AM E.T.
To be held virtually at
www.virtualshareholdermeeting.com/OCUL2023

MANAGEMENT

Antony Mattessich
President & Chief Executive Officer

Peter Jarrett, Ph.D.
Chief Scientific Officer

Donald Notman
Chief Financial Officer

Rabia Gurses Ozden, M.D.
Chief Medical Officer

Philip Strassburger, Esq.
General Counsel

Christopher White
Chief Business Officer

Karen-Leigh Edwards, Ph.D., M.B.A.
Senior Vice President, Technical Operations

Steve Meyers
Senior Vice President, Commercial

Tracy Smith
Vice President, Human Resources

Charles Blizzard
Vice President, Research & Development

Cassandra George, Esq.
Vice President, Deputy General Counsel, Chief Ethics & Compliance Officer

Nicole Oliynyk
Vice President, Regulatory Affairs

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Director of Vitreoretinal Service and Director of Retina Research | Ophthalmic Consultants of Boston

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President & COO / Co-founder | Cellemedy

Richard Lindstrom, M.D.
Founder / Director / Attending Surgeon | Minnesota Eye Consultants, P.A.

Merilee Raines
Director | Biotherapeutic Companies

Leslie J. Williams
President & Chief Executive Officer hC Bioscience, Inc.

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