UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 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, 2016

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: 001-36829

Inotek Pharmaceuticals Corporation

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**04-3475813**
(State or Other Jurisdiction of Incorporation or Organization)	**(IRS Employer Identification No.)**
91 Hartwell Avenue Lexington, MA	**02421**
(Address of Principal Executive Offices)	**(Zip Code)**

(781) 676-2100
(Registrant's Telephone Number, Including Area Code)

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.01 par value	**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 Exchange Act. Yes ☐ No ☒

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes ☒ No ☐

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

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

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☒

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

The aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold on June 30, 2016 was $43.8 million.

As of March 15, 2017, there were 26,986,318 shares of common stock, $0.01 par value per share, outstanding.

EXPLANATORY NOTE

The Company meets the "accelerated filer" requirements as of the end of its 2016 fiscal year pursuant to Rule 12b-2 of the Securities Exchange Act of 1934, as amended. However, pursuant to Rule 12b-2 and SEC Release No. 33-8876, the Company (as a smaller reporting company transitioning to the larger reporting company system based on its public float as of June 30, 2016) is not required to satisfy the larger reporting company requirements until its first

quarterly report on Form 10-Q for the 2017 fiscal year and thus remains eligible to use the scaled disclosure requirements applicable to smaller reporting companies under Item 10 of Regulation S-K under the Securities Act of 1933, as amended, in this Annual Report on Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “seek,” “should,” “target,” “will,” “would,” or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our anticipated cash needs and our estimates regarding our capital requirements and our needs for additional financing;
- federal, state, and non-U.S. regulatory requirements, including regulation of our current or any other future product candidates by the U.S. Food and Drug Administration (the “FDA”);
- the success, timing and cost of our current Phase 3 program for *trabodenoson* as a monotherapy and planned Phase 3 and other clinical trials and anticipated Phase 2 program for our fixed-dose combination product candidate, including statements regarding the timing of initiation and completion of the trials;
- the timing of and our ability to submit regulatory filings with the FDA and to obtain and maintain FDA or other regulatory authority approval of, or other action with respect to, our product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy, including with respect to our potential sales force in the United States and our partnering and collaboration efforts outside the United States;
- third-party payor reimbursement for our current product candidates or any other potential products;
- our expectations regarding the clinical safety, tolerability and efficacy of our product candidates and results of our clinical trials;
- the glaucoma patient market size and the rate and degree of market adoption of our product candidates by ophthalmologists, optometrists and patients;
- the timing, cost or other aspects of a potential commercial launch of our product candidates and potential future sales of our current product candidates or any other potential products if any are approved for marketing;
- our expectations regarding licensing, acquisitions and strategic operations;
- the potential advantages of our product candidates;
- our competitors and their product candidates, including our expectations regarding those competing product candidates;
- our ability to protect and enforce our intellectual property rights, including our patented and trade secret protected proprietary rights in our product candidates; and
- anticipated trends and challenges in our business and the markets in which we operate.

We caution you that the foregoing list may not contain all of the forward-looking statements made in this Form 10-K.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of therapies for glaucoma and other diseases of the eye. Glaucoma is a disease of the eye that is typically characterized by structural evidence of optic nerve damage, vision loss and consistently elevated intraocular pressure, or IOP. Our lead product candidate, *trabodenoson*, is a first-in-class selective adenosine mimetic that we rationally designed to lower IOP by restoring the eye's natural pressure control mechanism. We developed this molecule to selectively stimulate a particular adenosine subreceptor in the eye with the effect of augmenting the intrinsic function of the eye's trabecular meshwork, or TM. The TM regulates the pressure inside the eye and is also the main outflow path for the fluid inside of the eye that often builds up pressure in patients with glaucoma. We believe that by restoring the natural function of the TM and this outflow path, rather than changing the fundamental dynamics of pressure regulation in the eye, *trabodenoson*'s mechanism of action should result in a lower risk of unintended side effects and long term safety issues than other mechanisms of action. Additionally, *trabodenoson*'s unique mechanism of action in the TM should complement the activity of existing glaucoma therapies that exert their IOP-lowering effects on different parts of the in-flow and out-flow system of the eye.

Our product pipeline includes *trabodenoson* monotherapy delivered in an eye drop formulation, as well as a fixed-dose combination, or FDC, of *trabodenoson* with *latanoprost* given once-daily, or QD. We are also evaluating the potential of *trabodenoson* to slow the loss of vision associated with glaucoma and degenerative retinal diseases.

The recently completed Phase 3 pivotal trial, MATrX-1, did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute IOP from placebo at every single one of the 12 time points comprising the primary endpoint. This was due to a larger than expected treatment effect in the placebo/vehicle group, as compared to both our prior Phase 2 data and a recent meta-analysis examining placebo responses from 10 placebo-controlled trials, which showed a placebo/vehicle result of -2.01 mmHg (Raber, et al). During analysis of the IOP data from the trial, a treatment-by-site interaction was found where a small number of sites (4 sites out of a total of 55) caused an important change in the expected vehicle results. The review of the MATrX-1 data is ongoing and upon completion of all analyses, we plan to request a meeting with the U.S. Food and Drug Administration, or FDA, in the first half of 2017 to discuss these findings.

Statistically significant results for the primary endpoint of our completed Phase 2 clinical trial, and secondary endpoints of our completed MATrX-1 Phase 3 trial (Daily IOP Change from Diurnal Baseline and Analysis of Responders (subjects whose IOP decreased by >= 5 mmHg from baseline)), indicate that *trabodenoson* monotherapy has IOP-lowering effects, with a favorable safety and tolerability profile.

Our completed Phase 2 trial of *trabodenoson* co-administered with *latanoprost*, a prostaglandin analogue, or PGA, demonstrated IOP-lowering in patients who have previously had inadequate responses to treatment with *latanoprost*. These patients represent PGA poor-responders, as evidenced by persistently elevated IOP at levels that typically require the addition of a second drug to further lower IOP.

Upon successful completion of additional Phase 3 studies, we plan to submit a New Drug Application, or NDA, to the FDA for marketing approval of *trabodenoson* for the treatment of glaucoma in the United States. We plan to submit a marketing authorization application, or MAA, in Europe after filing our NDA for approval of *trabodenoson* in the United States.

According to the British Journal of Ophthalmology, there were an estimated 2.8 million Americans with glaucoma in 2010. Once glaucoma develops, it is a chronic condition that requires life-long treatment. PGAs are the most widely prescribed drug class for glaucoma and include the most widely prescribed glaucoma drug, *latanoprost*. When PGA monotherapy is insufficient to control IOP or is poorly tolerated, non-PGA products, such as beta blockers, alpha agonists and carbonic anhydrase inhibitors, are generally used either as an add-on therapy to the PGA or as an alternative monotherapy. Both PGAs and non-PGAs can cause adverse effects in the eye. In addition, non-PGA drugs can have adverse effects in the rest of the body and have been shown to have poor tolerability profiles. As a result, we believe there is a significant unmet need for a treatment that effectively lowers IOP by restoring outflow and the natural pressure control by the TM, that has a favorable safety and tolerability profile, and that works effectively in combination with other treatments.

Additionally, no existing treatments offer the potential to directly treat the underlying cause of glaucoma associated vision loss: the death of retinal ganglion cells, or RGCs, the nerve tissue in the retina that relays the visual signal to the brain. We believe that a drug with the potential to make these cells more resilient to the stress caused by glaucoma would achieve broad market acceptance as the treatment preferred among patients and physicians.

We own a large patent estate covering a wide range of countries and markets for our current product candidates and have patents and pending patent applications related to *trabodenoson* pharmaceutical compositions and methods of use for *trabodenoson*, certain of which can extend patent protection through to 2031 and 2034. If *trabodenoson* receives marketing approval in the United States, we plan to commercialize it by establishing our own specialty sales force in the United States.

Our Strategy

Our goal is to become a leading biopharmaceutical company focused on the discovery, development and commercialization of novel therapies to treat glaucoma. The key elements of our strategy are as follows:

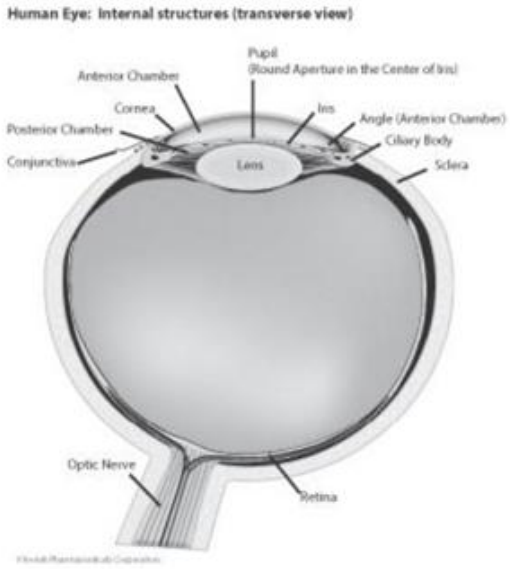
- ***Complete clinical development and seek marketing approval for our lead product candidate, trabodenoson monotherapy***. In 2012, we completed a Phase 2 trial of *trabodenoson* monotherapy, which demonstrated statistically significant IOP-lowering and a favorable safety profile. We had an End-of-Phase 2 meeting with the FDA in 2015 to discuss our Phase 3 program for *trabodenoson* monotherapy and to confirm the design and endpoints for the Phase 3 pivotal trials. At the meeting, we reached agreement on the design of our initial Phase 3 study, as well as the overall regulatory path for *trabodenoson*. We completed our initial Phase 3 pivotal trial, MATrX-1, and reported top-line data on January 3, 2017. MATrX-1 did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute IOP from placebo at every single one of the 12 time points comprising the primary endpoint. The review of the MATrX-1 data is ongoing and upon completion of all analyses, we plan to request a meeting with the FDA in the first half of 2017 to discuss both these findings and the subsequent necessary steps needed to attain marketing approval of *trabodenoson* monotherapy for the treatment of glaucoma in the United States. If we file an NDA for approval of *trabodenoson* monotherapy in the United States, we plan to submit an MAA in Europe.
- ***Complete clinical development and seek marketing approval of a fixed-dose combination product that includes both trabodenoson and latanoprost***. As many as half of glaucoma patients, typically those with more severe disease, need to use two or more glaucoma drugs to sufficiently reduce their IOP. The initial treatment for glaucoma patients is usually the use of a prescription eye drop from the PGA drug class. However, as PGAs are often unable to lower IOP sufficiently to reach the patient's medically targeted level, non-PGA products are used either as an add-on therapy to the PGA or as an alternative monotherapy in place of PGAs. There are currently no FDC products approved for use in the United States that include a PGA. We intend to formulate and conduct clinical development in order to seek marketing approval for an FDC product that includes both *trabodenoson* and *latanoprost*, the best-selling PGA. We believe that the favorable safety and tolerability profile and complementary mechanism of action of *trabodenoson* could, if approved, make an FDC with *latanoprost* a highly effective, well-tolerated and more convenient QD regimen for treating glaucoma in patients who have a less functional TM and therefore need additional help lowering their IOP. Our completed Phase 2 trial of *trabodenoson* co-administered with the PGA, *latanoprost*, demonstrated IOP-lowering in patients who have previously had inadequate responses to the PGA, *latanoprost*. These patients represent PGA poor-responders, as evidenced by persistently elevated IOP at levels that typically require the addition of a second drug to further lower IOP.
- ***Establish a specialty sales force to maximize the commercial potential of trabodenoson in the United States***. We have retained worldwide commercial rights to *trabodenoson*. If *trabodenoson* receives marketing approval in the United States, we plan to commercialize it by establishing a glaucoma-focused specialty sales force of approximately 150 people targeting ophthalmologists and optometrists throughout the United States. For markets outside the United States, we intend to explore partnership opportunities through collaboration and licensing arrangements.
- ***Evaluate the potential of trabodenoson and other assets to slow the loss of vision associated with glaucoma and degenerative retinal diseases or for additional ophthalmic indications.*** Based on an animal model that indicated *trabodenoson*'s potential to directly protect RGCs, the nerve tissue in the retina that relays the visual signal to the brain, we plan to conduct clinical trials to measure the rate of vision loss over time, rather than IOP control, in patients treated with *trabodenoson*. Should the results of these trials be positive, we plan to seek labeling indicative of *trabodenoson*'s potential to change the course of glaucoma-related vision loss, beyond that of IOP-lowering effect alone. In addition, this effect, if proven, could address the subset of glaucoma patients that do not have high IOPs, but still suffer from vision loss over time. We are also evaluating other potential indications where therapy with *trabodenoson* may be beneficial. To begin this process, we are conducting pre-clinical trials for optic neuropathies and degenerative retinal diseases. In addition, we are evaluating other preclinical assets in additional ocular indications.

Glaucoma Overview

Glaucoma is a disease of the eye in which damage to the optic nerve leads to progressive, irreversible vision loss. Its characteristics can include structural evidence of optic nerve damage, vision loss and consistently elevated IOP.

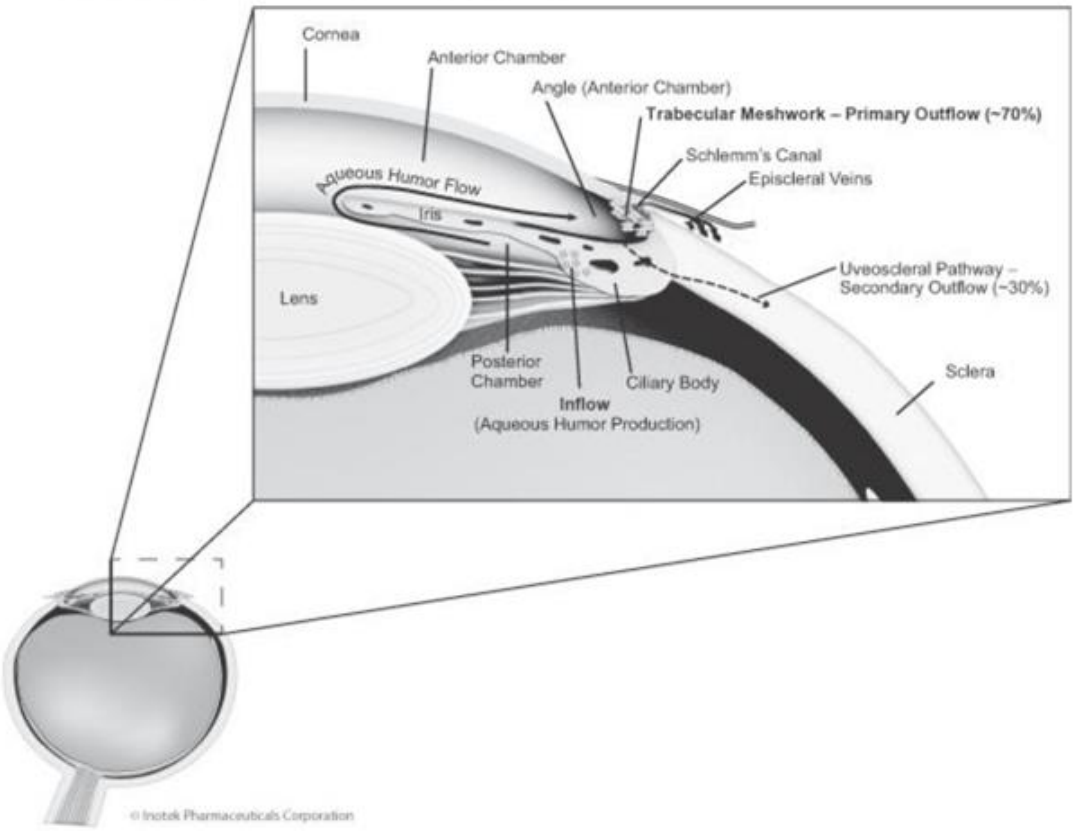
Physiology of the Eye

The eye is a fibrous sack which must stay “inflated” with a fluid that maintains the eye’s form, known as aqueous humor, at the proper pressure in order to maintain its shape and effectively focus light to the retina where the light stimulus is then relayed to the brain and converted into a visual image. To maintain the eye’s pressure—and therefore its shape—and as a means to provide nutrients to eye tissue, aqueous humor is constantly produced inside the eye by a tissue known as the ciliary body. The ciliary body sits just behind the iris, which is the colored part of the eye. Aqueous humor flows forward through a hole in the center of the iris, called the pupil, and down into the angle defined by the front of the iris and the back of the cornea, which is the clear covering on the front of the eye. This angle is the same angle referred to in Primary Open Angle Glaucoma, or POAG, the most common form of glaucoma. Below is a diagram depicting certain parts of the eye, including the ciliary body, iris and the angle defined by the front of the iris and the back of the cornea:



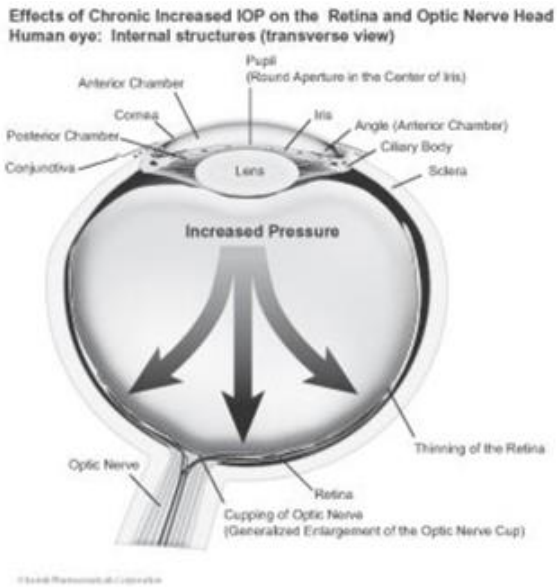
In this angle, in front of the outer rim of the iris, is the TM, a natural, pressure-regulating drain. It is here that in a healthy, well-functioning eye, approximately 70% of the aqueous humor exits and flows into a drainage canal known as Schlemm's canal, which empties back into the venous drainage system. The remaining approximately 30% of the aqueous humor leaves the eye through a secondary pathway called the uveoscleral pathway. The diagram below reflects the TM and the uveoscleral pathway, the two pathways for the aqueous humor to leave the eye.

Trabecular Meshwork and Aqueous Humor Dynamics



Development of High IOP and its Effects on Glaucoma

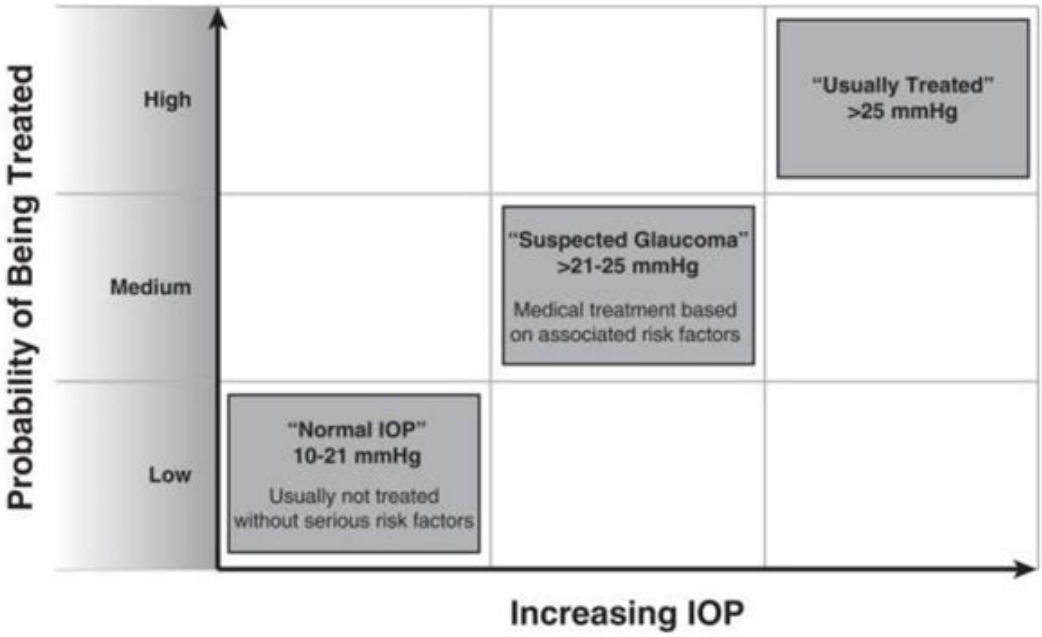
In a typical glaucoma patient, there is resistance to drainage of the aqueous fluid (i.e., not enough aqueous humor exits the eye), creating excess pressure and compressing the retina, the layer of tissue covering the inside of the back half of the eye that actually converts light into nerve impulses. For people to "see," these impulses—the visual signal—must be relayed through the optic nerve back to the brain for processing. The cells in the retina require nutrients and oxygen that are delivered via blood vessels entering and exiting the eye through the same opening as the nerve fibers carrying the visual signal. However, when IOP is too high, it is more difficult to pump blood enriched in oxygen and nutrients into the retina. The diagram below reflects the anatomy of the eye and how elevated IOP can impair the nerve tissue in the retina and the optic nerve head.



The deprivation of blood supply to the retina may damage RGCs, the nerve tissue in the retina that relays the visual signal to the brain. These RGCs have long tails called axons that extend back to the brain to carry the visual image. In fact, the optic nerve is nothing more than a bundle of these axons extending to the vision processing center of the brain. When an RGC dies, one of the connections between the retina and the brain is lost, and like most cases when a nerve is damaged or cut—like in a spinal cord injury—there is no known way to repair the damage and, as a result, some portion of vision is permanently lost. Therefore, the root cause of vision loss in glaucoma is not high IOP per se, but the impact of high IOP on the retina, and specifically the RGCs.

Clinical Definition of Glaucoma

There are two key elements to the clinical definition of glaucoma: structural evidence of optic nerve damage and vision loss. Common risk factors include age, family history, corneal thickness and high IOP, commonly measured in millimeters of mercury, or mmHg. Currently, the only known way to treat glaucoma and slow the progression of vision loss is to reduce IOP. While treatment approaches are based on an assessment of the patient's risk factors for vision loss, elevated IOP is by far the best understood contributor to development of glaucoma. We believe that the general treatment patterns in the figure below, relative to a patient's IOP, are typical.



The Ocular Hypertension Treatment Study, or the OHTS, was a large, randomized academic trial published in 2002 that followed a total of 1,636 participants who initially had no evidence of glaucoma-related damage. The OHTS found that higher IOPs generally indicate a higher risk for progression to glaucoma. An IOP of 10 to 21 mmHg is generally considered in the normal range. Individuals with IOPs greater than 21 and up to 25 mmHg will often not be prescribed drug therapy unless they have evidence of both structural changes and some vision loss, or some combination of these and other risk factors for future vision loss. In fact, the United Kingdom's National Institute of Health and Care Excellence Guidelines, or NICE Guidelines, for the treatment of suspected glaucoma (structural changes but without vision loss) plus elevated IOP, does not recommend treatment of eyes with corneal thickness of 555-590 nm and IOP of 25 mmHg or below. Drug treatment is much more common when patients have IOPs greater than 25 mmHg.

Glaucoma Market

According to the British Journal of Ophthalmology, there were an estimated 2.8 million Americans with glaucoma in 2010. According to the Archives of Ophthalmology, that number will reach approximately 3.4 million by 2020. Approximately 120,000 of these patients are suffering from blindness as a result of destruction to their optic nerve. Glaucoma can affect patients of all ages and ethnicities. However, according to the Archives of Ophthalmology, the prevalence rate (the proportion of people in the population that have glaucoma) increases with age. The most significant increases in prevalence rates occur above 55 years of age. The prevalence in the population aged 65 years and younger is approximately twice that of the population 55 years or younger. Glaucoma is a chronic condition with no known cure and as a result patients are typically treated for the rest of their lives. Patients with glaucoma report decreased quality-of-life, difficulties with daily functioning, including driving, and are more likely to report falls and motor vehicle collisions.

According to IMS Health, sales of glaucoma drugs in 2013 were approximately $2.0 billion in the United States and $5.6 billion worldwide and 31.2 million prescriptions were written for glaucoma medications in the United States. According to IMS Health, approximately two-thirds of these prescriptions were for generic drugs, including *latanoprost* and *timolol*, which are the top two selling drugs for the treatment of glaucoma. Due to the lack of innovation in medications for glaucoma, most of the drugs used to treat glaucoma are generic drugs. IMS Health projects U.S. sales of glaucoma drugs to be $3.1 billion in 2018, an increase of approximately 54% over 2013 sales.

Existing Glaucoma Treatments

The initial treatment for glaucoma patients is typically the use of a prescription eye drop from a class of drugs called PGAs. According to IMS Health, prescriptions for PGAs make up more than half of all prescriptions for glaucoma medications. The PGAs' primary mechanism of action for treating glaucoma is thought to be increasing fluid outflow through the uveoscleral pathway. A number of adverse effects are known to occur in all drugs in the PGA class and, as a result, these side effects are assumed to be associated with the mechanism of action. Most notable of these side effects is eye redness, or conjunctival hyperemia.

When PGAs are insufficient to control IOP or are poorly tolerated, non-PGA products are used either as an add-on therapy to the PGA or as an alternative monotherapy in place of a PGA. Non-PGAs can include a beta-blocker, an alpha (adrenergic) agonist or a carbonic anhydrase inhibitor alone. FDC products containing these non-PGAs are dominated by beta-blocker combinations, which can take the form of a beta-blocker combined with an alpha agonist (Combigan®), or a beta-blocker combined with a carbonic anhydrase inhibitor (Cosopt® or generic equivalent). Finally, there is a non-PGA combination (Simbrinza®) which consist solely of an alpha agonist and a carbonic anhydrase inhibitor. Non-PGA drugs generally have poorer tolerability in the eye than PGA drugs, and some have systemic adverse effects that limit the patient population in which they can be used safely. Moreover, their IOP-lowering effect is generally less than that of PGAs and the vast majority of non-PGAs are required to be dosed multiple times daily.

The existing classes of treatment available for glaucoma each have varying mechanisms of action, levels of IOP-lowering, side effects and other adverse effects, as described in the following table.

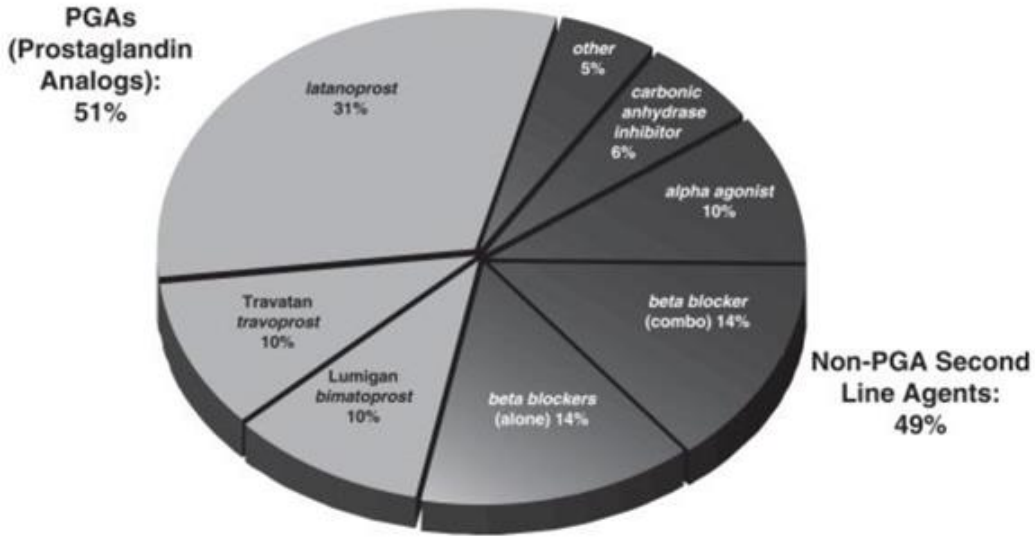
Summary of Existing Glaucoma Treatments:

Drug Classification *(Generic Names)*	Mechanism of Action*	IOP Reduction**	Known Side Effects*	Other Precautions, Warnings, Contraindications and Adverse Effects*
Prostaglandin analog *latanoprost* Travatan *(travoprost)* Lumigan *(bimatoprost)*	Increase uveoscleral and/or trabecular outflow	6-8 mmHg (25%-33%)	- Eye redness (conjunctival hyperemia) - Visual disturbances (blurred vision, loss of visual acuity) - Itching (pruritis) - Burning - Stinging - Eye pain - Darkening of the eyelids (periocular hyperpigmentation) - Permanent eye (iris) color change	- Macular edema - History of herpetic keratitis - Ocular edema
Beta-adrenergic antagonist, or beta-blocker *timolol*	Decrease aqueous production	N/A mmHg (20%-25%)	- Burning - Stinging - Eye lid swelling (Blepharitis) - Corneal inflammation (keratitis) - Itching (pruritis) - Eye pain - Dry eyes, foreign body sensation - Visual disturbances - Drooping eye lids (ptosis) - Swelling of retina (cystoid macular edema)	- Muscle weakness - Anaphylaxis - Severe respiratory and cardiac reactions - Contraindicated in bronchial asthma (or history of), severe chronic obstructive pulmonary disease, sinus bradycardia (slower heart rate), second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock
Alpha-adrenergic agonist, or alpha agonist *brimonidine*	Decrease aqueous production; increase uveoscleral outflow	2-6 mmHg (20%-25%)	- Allergic conjunctivitis - Eye redness (conjunctival hyperemia) - Itchy eyes (eye pruritis)	- Severe cardiovascular disease - Depression - Cerebral or coronary insufficiency - High blood pressure (orthostatic hypertension) - Contraindicated in patients on monoamine oxidase inhibitor therapy
Carbonic anhydrase inhibitor dorzolamide *brinzolamide*	Decrease aqueous production	3-5 mmHg (15%-20%)	- Bitter taste - Burning - Stinging - Allergic conjunctivitis - Corneal inflammation (superficial punctate keratitis)	- Conjunctivitis - Eye lid reactions - Sulfonamide allergy

* According to FDA-approved labeling.

** mmHg, according to FDA-approved labeling; % from baseline, according to American Academy of Ophthalmology Glaucoma Panel.

The chart below illustrates the respective proportions of glaucoma prescriptions issued in 2013 by class, according to IMS Health.



Glaucoma Treatments Currently in Development.

We believe there are currently two leading classes of new drugs in clinical development for glaucoma: Rho kinase inhibitors and adenosine mimetics.

A Rho kinase inhibitor is currently in Phase 3 clinical trials and is the furthest along of the potential new glaucoma drug therapies: Aerie Pharmaceuticals, Inc.'s AR-13324. Like with PGAs, conjunctival hyperemia has been reported with the Rho kinase inhibitor class.

Adenosine mimetics are compounds that mimic or simulate some of the actions or effects of adenosine, a naturally-occurring molecule with many, diverse biologic effects. There are four known subreceptors that are specific to adenosine: A1, A2a, A2b and A3. These subreceptors can cause many effects if stimulated. In the adenosine mimetic group, there are compounds targeting three different adenosine subreceptors: A1, A2a and A3. We believe that A1 selectivity is necessary for optimal IOP-lowering effect. To our knowledge, the two compounds being developed by other companies that were selective for the A2a subreceptor have been discontinued from clinical development for glaucoma. A third compound being developed that we believe targets both the A1 (IOP-lowering) and the A3 (IOP-increasing) subreceptors is still being studied. We believe that because this third compound is dosed orally, it is challenging to isolate its pharmacologic effects solely to the eye. We believe we are the only company to be developing an adenosine mimetic highly selective for the A1 subreceptor for ophthalmic indications.

Market Opportunity

Since 1996, there have been no new drug classes approved in the United States for glaucoma. As a result, there are persistent inadequacies in the tools that ophthalmologists use to manage patients with glaucoma. Thus, we believe there is a need for an innovative glaucoma treatment that offers:

- significant IOP-lowering;
- a favorable safety and tolerability profile;
- a novel mechanism of action that complements existing therapies; and
- convenient dosing.

Our Solution—*Trabodenoson*

Trabodenoson is a first-in-class selective adenosine mimetic that is designed to lower IOP with a mechanism of action that we believe augments the natural function of the TM. In addition, by enhancing a naturally occurring process to make the eye function more like that of a younger, healthier eye, rather than changing the fundamental dynamics of pressure regulation in the eye, we believe there is a lower risk of unintended side effects that could result in safety or tolerability issues in the long term. We believe *trabodenoson* enhances metabolic activity in the TM, which helps clear the pathway for the aqueous humor, the fluid in the eye, to flow out of the eye, thereby lowering IOP. We believe that *trabodenoson*'s mechanism of action improves the function of the eye, and that *trabodenoson* has the potential to be used as a monotherapy in place of current glaucoma treatments. In addition, we expect that *trabodenoson*'s purported mechanism of action in the TM should complement the activity of all currently-approved glaucoma drugs that work in other ways to lower IOP.

We believe the following elements of *trabodenoson*'s product profile will drive its adoption, if approved, in the glaucoma market:

- *Meaningful IOP-Lowering.* After three months of monotherapy treatment in a Phase 3 clinical trial, MATrX-1, in glaucoma patients who had discontinued any other medications, trabodenoson (500 mcg) lowered IOP by an average of 4.25 mmHg from diurnal baseline. Moreover, daily average IOP reduction was statistically significantly greater than placebo at days 84, 42, and 14, with marginal significance at day 28. MATrX-1 did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute IOP from placebo at every single one of the 12 time points comprising the primary endpoint. This was due to a larger than expected treatment effect in the placebo/vehicle group, as compared to both our prior Phase 2 data and a recent meta-analysis examining placebo responses from 10 placebo-controlled trials, which showed a placebo/vehicle result of -2.01 mmHg (Raber, et al). During analysis of the IOP data from the trial, a treatment-by-site interaction was found where a small number of sites (4 sites out of a total of 55) caused an important change in the expected vehicle results. The review of the MATrX-1 data is ongoing and upon completion of all analyses, we plan to request a meeting with the FDA in the first half of 2017 to discuss these findings.

- *Favorable Safety Profile.* Prior to MATrX-1, in four completed *trabodenoson* clinical trials over a wide range of doses, no patients had been withdrawn due to a *trabodenoson*-related side effect in the eye. In our multiple-dose Phase 3 MATrX-1 monotherapy clinical trial, drug-related dropouts were 1.1 % of patients across all doses tested. Furthermore, in our completed multiple-dose Phase 2 trial of *trabodenoson* co-administered with *latanoprost* in a population of PGA poor-responders, there also was no change in the rate of hyperemia from study baseline after four, eight or 12 weeks of treatment. No systemic effects of the drug have been identified, despite rigorous monitoring including cardiac and renal function, when administered as an eye drop. We believe this safety profile could be important in the potential for *trabodenoson* to become a preferred treatment alternative for patients that experience undesired side effects with existing therapies.

- *Unique, Complementary Mechanism of Action.* We believe that *trabodenoson*'s mechanism of action augments a naturally occurring process by clearing the path for aqueous humor outflow in the TM. We expect that this mechanism of action should complement all currently-approved glaucoma drugs which work in other ways to lower IOP, including by reducing aqueous humor production and increasing outflow through the uveoscleral pathway. This complementary mechanism was confirmed in patients already receiving *latanoprost* therapy in a recently completed multiple-dose Phase 2 trial. In this Phase 2 trial of *trabodenoson* co-administered with *latanoprost* in a population of PGA poor-responders, patients on *latanoprost* experienced an additional 5.8 mmHg IOP lowering from their study baseline and 4.3 mmHg from their diurnal baseline after 12 weeks treatment (eight weeks BID plus four weeks QD). These results make *trabodenoson*, with its favorable safety profile, a candidate to add to other glaucoma medications when a further reduction of the IOP is desirable.

- *Convenient Dosing.* Current Phase 2 clinical data indicate that QD dosing with *trabodenoson* in PGA poor-responders is well tolerated and lowers IOP significantly. We believe a QD dosing regimen minimizes the burden on patients to remember to take their medication, thus, we believe, potentially improving compliance with the therapy. If confirmed and approved in our Phase 3 program, QD dosing would make *trabodenoson* easier to use than most non-PGA products, and *trabodenoson*'s dosing frequency would match the best-in-class PGAs, which would facilitate an FDC with a PGA that could be dosed QD.

We believe that *trabodenoson*'s IOP-lowering results, complementary mechanism of action, dosing and safety profile make it well suited for use in an FDC with a PGA, which could be a convenient option for patients currently using two or more glaucoma drugs to lower IOP.

Trabodenoson Discovery—Background

Adenosine is a naturally occurring molecule that has a broad array of biological effects. Its effects are mediated through activity at four known adenosine-specific subreceptors: A1, A2a, A2b and A3. These subreceptors are present throughout the body on the cells of different tissues, and at different concentrations. When adenosine binds and activates these different subreceptors, it can cause many diverse effects.

In 1995, a study was published in the Journal of Pharmacology and Experimental Therapeutics describing how adenosine mimetics can lower IOP by activating adenosine A1 subreceptors in rabbits. In 2001, an animal study published by the University of Pennsylvania School of Medicine confirmed that stimulation of A1 lowered IOP, but that stimulating A2a or A3 subreceptors increased IOP.

Our scientists began a rational deconstruction of this complex biology in order to isolate the protective activity of adenosine and to incorporate it into novel therapeutics. Beginning with the structure of adenosine, we created a series of molecules to bind with, and therefore induce the biological effects associated with stimulation of a single adenosine subreceptor. In this way, the undesired biological actions of native adenosine were systematically removed, one by one by eliminating the activity at non-target subreceptors. This rational drug design process relied heavily on our understanding of structure activity relationships, which relate the variation in the structure of the adenosine mimetics and their ability to bind and activate ideally just one adenosine subreceptor. Ultimately, a number of molecules emerged from these efforts with isolated and specialized activity, including some adenosine mimetics that only targeted the A1 subreceptor, leading to the discovery of *trabodenoson*.

The high affinity binding of *trabodenoson* to the A1 subreceptor is shown by the small Ki in the table below, and its selectivity for this IOP-lowering activity is indicated by much higher Ki's for A2a and A3 receptors where its binding is relatively weak.

Trabodenoson is a Potent and Selective A1 Adenosine Mimetic

Compound	A1 (Ki, nM)	A2a (Ki, nM)	A3 (Ki, nM)	Selectivity Ratios A2a/A1	Selectivity Ratios A3/A1
Trabodenoson	0.97	4,690	704	4,835x	725x

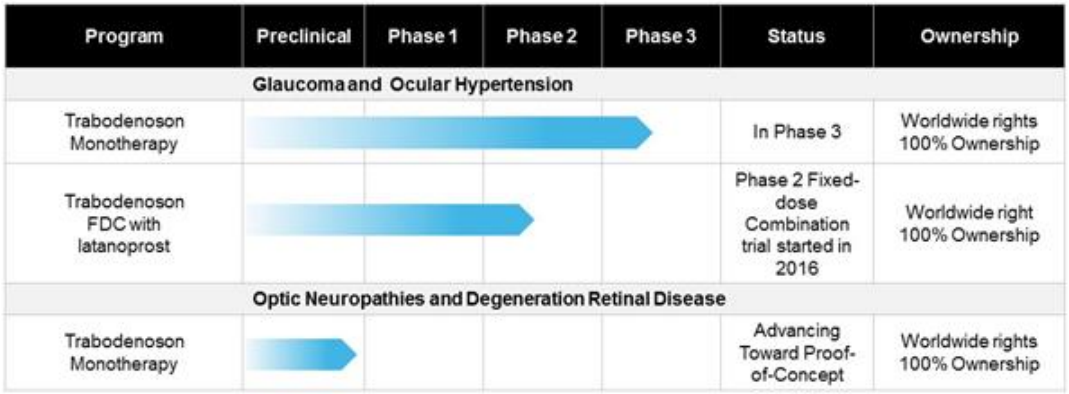
Trabodenoson's key characteristics include:

1. Potency—Ki in single-digit nM range (0.97nM);
2. High Selectivity—over A2a> 1000-fold and A3>500-fold;
3. Ease of Fat Solubility—allowing corneal penetration so it can reach the TM; and
4. A high compatibility with the often sensitive tissues in the front of the eye.

We believe that *trabodenoson* is the only adenosine mimetic with high selectivity for the single desired target of action, the A1 subreceptor, and that stimulation of this subreceptor in the TM effects a meaningful improvement in the metabolic activity in the TM that helps to clear the pathway for the aqueous humor to flow out of the eye, lowering IOP. This metabolic activity takes the form of an increase or up-regulation of proteases—such as Protease A or MMP-2—that digests and removes accumulated proteins that can block the healthy flow of the aqueous humor out of an eye with glaucoma. This metabolic activity is a naturally occurring or endogenous process that is enhanced by treatment with *trabodenoson*. We believe this process does not radically change the way the TM controls eye pressure, but rather restores the natural process of pressure control in the TM, which is different from other therapies that decrease aqueous humor production or increase the permeability of the eye to increase outflow.

Product Pipeline

Our product pipeline includes *trabodenoson*, as a monotherapy delivered in an eye drop formulation, as well as an FDC that includes *trabodenoson* plus *latanoprost* in an eye drop formulation, which we refer to as our FDC product candidate. We are also evaluating the potential for *trabodenoson* to directly target optic neuropathies and degenerative retinal diseases. The following table summarizes key information about our product development programs.



Trabodenoson

Our first product candidate, trabodenoson, is a monotherapy dosed in an eye drop. Our clinical trials have shown that trabodenoson has significant IOP-lowering effects, convenient dosing and a favorable safety profile when compared to the currently available glaucoma treatments, such as PGAs and non-PGAs. MATrX-1 did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute IOP from placebo at every single one of the 12 time points comprising the primary endpoint. This was due to a larger than expected treatment effect in the placebo/vehicle group, as compared to both our prior Phase 2 data and a recent meta-analysis examining placebo responses from 10 placebo-controlled trials, which showed a placebo/vehicle result of -2.01 mmHg (Raber, et al). During analysis of the IOP data from the trial, a treatment-by-site interaction was found where a small number of sites (4 sites out of a total of 55) caused an important change in the expected vehicle results. The review of the MATrX-1 data is ongoing and upon completion of all analyses, we plan to request a meeting with the FDA in the first half of 2017 to discuss these findings.

Trabodenoson-Latanoprost Fixed-Dose Combination

Our second product candidate is a combination of *trabodenoson* with a PGA, *latanoprost*, to create an FDC. As many as half of glaucoma patients, typically those with more severe disease, need to use two or more glaucoma drugs to sufficiently reduce their IOP. The available FDC products increase IOP-lowering but also have unpleasant tolerability challenges in the eye, as well as the adverse effects, safety warnings, precautions and contraindications that the two individually-dosed drugs carry in their FDA-approved package inserts. An FDC product containing a PGA plus a non-PGA has not yet been approved in the United States. We believe that none have gained FDA approval because the modest incremental benefit in IOP-lowering seen when a non-PGA is added to a PGA is too small in the context of the added side effects and clinical risks that come with the combined drugs. In contrast, based on our completed Phase 2 study in which *trabodenoson* therapy was co-administered with *latanoprost*, we believe that an FDC containing a PGA and *trabodenoson* would be well received in the glaucoma market, especially for use in patients with higher IOPs that currently use two or more glaucoma drugs to lower IOP.

We expect that *trabodenoson* will not adversely affect the safety profile of *latanoprost*, or any other currently-approved PGA, because of its favorable safety and tolerability profile from our completed Phase 2 trial in which *trabodenoson* and *latanoprost* were co-administered. We believe that *trabodenoson*'s mechanism for lowering IOP complements the mechanism of action of *latanoprost* and other PGAs, which work primarily on the secondary uveoscleral outflow, because *trabodenoson* is believed to act through the TM, the largest aqueous humor outflow path in the eye. In fact, our IOP-lowering studies in cynomolgus monkeys have shown that IOP-lowering is significantly better when the eye is treated with both *trabodenoson* and *latanoprost*, as compared to treatment with *latanoprost* alone.

Our completed Phase 2 trial of trabodenoson co-administered with *latanoprost* also demonstrated IOP-lowering in patients who have previously had inadequate responses to *latanoprost*. These patients represent PGA poor-responders, as evidenced by persistently elevated IOP at levels that typically require the addition of a second drug to further lower IOP. The safety profile of trabodenoson co-

administered with *latanoprost* is similar to that of trabodenoson monotherapy. Moreover, trabodenoson had a sufficiently long duration of action, allowing it to be effectively dosed QD in conjunction with *latanoprost*. Assuming the trabodenoson safety profile remains favorable, a trabodenoson-*latanoprost* FDC therapy could present a much improved risk/benefit profile over other combinations of currently-approved PGAs and non-PGAs. Currently, a Phase 2 dose-ranging, fixed-dose combination trial investigating combinations of trabodenoson and *latanoprost* in a single eye drop is ongoing. Results are anticipated in mid-2017.

Trabodenoson for Optic Neuropathy and Degenerative Retinal Diseases

The neuroprotective potential of *trabodenoson* is supported by the basic biology of adenosine, which has shown that the stimulation of the A1 receptor can protect tissues of the central nervous system. A pre-clinical study of the impact of high IOP on RGCs showed that *trabodenoson* could protect this key population of cells in the retina that, when lost, result in the irreversible vision loss associated with glaucoma. While we have not yet conducted a formal program of studies to prove neuroprotection, we plan to study the potential of *trabodenoson* monotherapy and our FDC product candidate to slow the loss of vision significantly more than attributable to IOP lowering alone, either in glaucoma patients or in other rarer forms of optic neuropathies.

Clinical Data and Development Strategy

Our Phase 3 program for *trabodenoson* as a monotherapy incorporates the FDA-acceptable clinical endpoint of IOP, in studies with three months of treatment. We had an End-of-Phase 2 meeting with the FDA in 2015 to discuss our Phase 3 program for *trabodenoson* monotherapy, and to confirm the design and endpoints for the Phase 3 pivotal trials. At the meeting, we reached agreement on the design for our initial Phase 3 study, as well as the overall regulatory path for *trabodenoson*. The trial design for the initial Phase 3 study was a five-arm superiority trial including three doses of *trabodenoson*. The primary endpoint of the study was IOP, determined at four timepoints during the day, after 4, 6 and 12 weeks of treatment. The IOP of the *trabodenoson* treated subjects was statistically compared to those of placebo treated subjects. A timolol arm was included for study validation, but not for statistical comparison.

We initiated our Phase 3 program for *trabodenoson* monotherapy in October 2015 and reported top-line data from the first pivotal trial in the program on January 3, 2017. While MATrX-1 did not meet its primary endpoint, it did demonstrate efficacy as compared to placebo. We are planning to complete the analyses of this trial, then request a meeting with the FDA in the first half of 2017 to discuss these findings.

We are planning to commence our Phase 3 program for the FDC of *trabodenoson* and *latanoprost* in 2018.

Clinical Results

MATrX-1 Trabodenoson Phase 3 Tolerability, Safety and Efficacy of Monotherapy in Glaucoma Patients

MATrX-1 was a Phase 3 randomized, double-masked, placebo-controlled trial of trabodenoson in approximately 300 subjects diagnosed with POAG or OHT. MATrX-1 assessed the efficacy, safety and tolerability of trabodenoson over three months of treatment. The primary endpoint was reduction of IOP as compared to the placebo treatment arm. In addition, the study contained a timolol 0.5% arm to validate the sensitivity of the patient population and serve as an internal control. IOP was measured at four time points during the day: 8AM, 10AM, 12PM, and 4PM on Days 14, 28, 42 and 84. Three doses of trabodenoson ophthalmic suspension were administered: 3%/1000 mcg once daily, 4.5%/1500 mcg twice daily, and 6%/2000 mcg once daily. The trial enrolled patients with a diagnosis of POAG or OHT and an IOP greater than or equal to 24 mmHg and less than or equal to 34 mmHg.

In early 2017 we announced the results of MATrX-1. The results showed a skewed distribution of the IOP data resulting from outliers, as identified from histogram and distribution statistics. To minimize their effects, a statistical approach using medians was considered more appropriate than an approach primarily based on means. Therefore, the analyses of IOP were performed using median data.

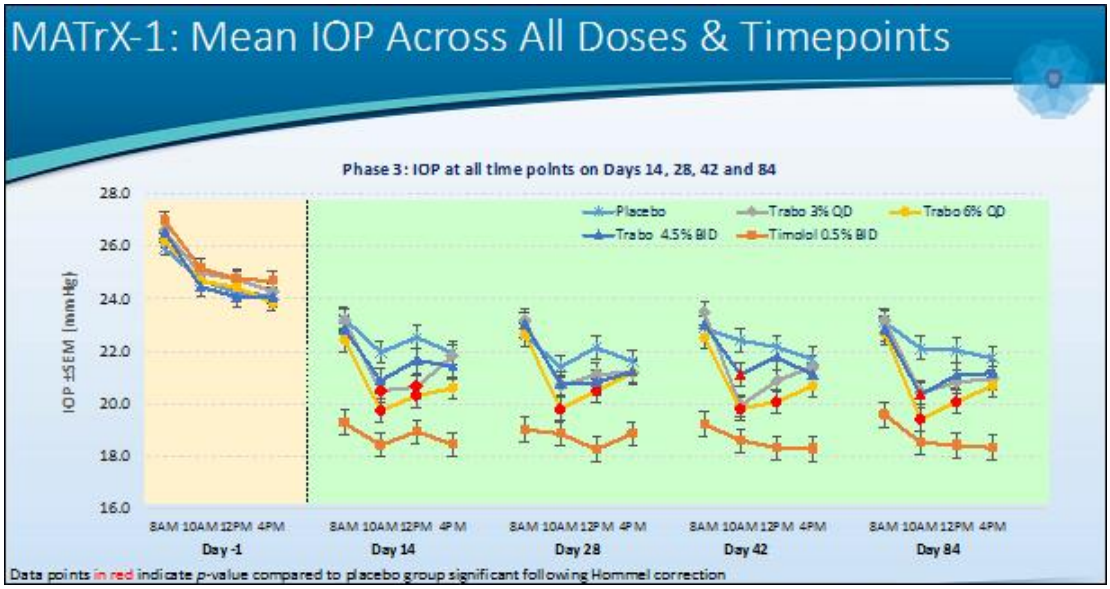
Results

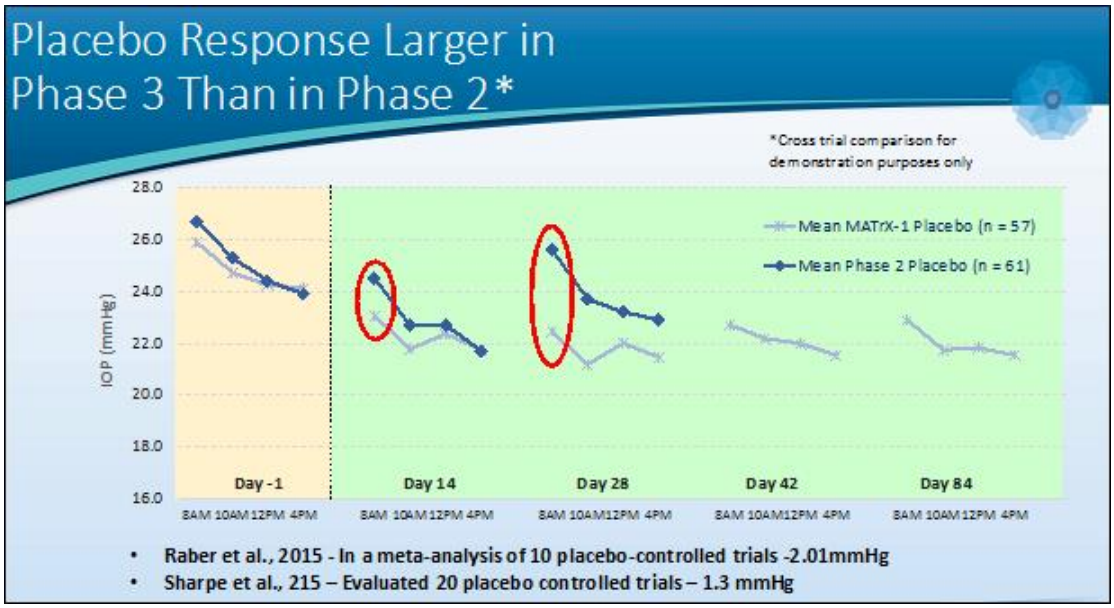
Total subjects randomized and treated was 300. The demographics of the trial were well balanced with a distribution of roughly 2/3rd POAGs to 1/3rd OHT subjects. Mean baseline IOPs ranged from 26.3 to 26.8 mmHg for all groups except for the timolol group which had a baseline IOP of 27.4 mmHg, as shown below.

	Trabo 4.5% BID	Trabo 6% QD	Trabo 3% QD	Overall Trabo	Placebo	Timolol
Randomized	57	61	64	182	62	57
ITT	56	61	64	181	62	57
Completers	49	57	59	165	55	54
Discontinuations	8(14%)	4(6.6%)	5(7.8%)	17(9.3%)	7(11.3%)	3(5.3%)
Age	63.9	63	64.8	63.9	63.3	64.2
POAG	66.1%	65.6%	64.1%	65.2%	62.9%	63.2%
OHT	33.9%	34.4%	35.9%	34.8%	37.1%	36.8%
Baseline IOP Mean/Median	26.8/26	26.3/26	26.4/26	26.5/26	26.4/26	27.4/26.5

Efficacy

The data showed that trabodenoson 6% once-a-day (QD) was the most effective dose, with IOP lowering that was comparable to that observed in Phase 2. Average Daily IOPs Change from Diurnal baseline at all days tested were statistically significantly lower than placebo, and the overall efficacy of the 6% QD dose was approximately 4.25 mmHg at the end of the study. While the trial did not meet its primary endpoint of demonstrating statistical separation from placebo/vehicle on three days (each with four IOP time points) for a total of twelve time points throughout the trial (see below); this was primarily due to two factors: a placebo response that was substantially greater than that observed in Phase 2 (see below), and 4 ‘outlier’ sites out of a total 55 sites that had results well outside of the range of other sites.





These 4 ‘outlier’ sites had a few subjects (n=5) randomized to the placebo arm with extreme placebo/vehicle responses that were clearly outside the norm or expected physiology. When all the data (from active as well as placebo subjects) from these 4 ‘outlier’ sites were removed from the analyses, despite a reduction in the overall sample size by 29 subjects, statistical significance was greatly increased, as shown below. This indicates the strong confounding effect of these few, but extreme placebo/vehicle outliers on the efficacy results.

MMRM on IOP by Visit and Time Point (Ranked Data) – Excluding (4) Outlier Sites

INOTEK

Trabodenoson 6% vs. Placebo

P-values	Day 14	Day 28	Day 42	Day 84
8am	0.0097	0.0554	0.0313	0.0452
10am	<0.0001	<0.0001	<0.0001	<0.0001
12pm	<0.0001	<0.0001	<0.0001	0.0003
4pm	<0.0001	0.0224	0.0013	0.0299

Safety

All doses of *trabodenoson* were well-tolerated, with approximately 1.6% of patients discontinuing the study due to drug-related side effects. There were no serious adverse events, or SAEs, related to trabodenoson. Consistent with prior trials, no evidence of significant systemic effects was observed. Notably, hyperemia was comparable between the trabodenoson and placebo arms. Also, there were no reports of drug-related eye pain, itching or irritation in any of the trabodenoson arms.

Trabodenoson Phase 2 Tolerability, Safety and Efficacy of Monotherapy in Glaucoma Patients

In 2012, we completed a successful Phase 2 dose-ranging clinical trial in 144 patients with OHT (ocular hypertension with no visual field loss) or POAG, which demonstrated a clear dose response to *trabodenoson*. Statistically significant results for the primary endpoint of our Phase 2 clinical trials indicate that *trabodenoson* has IOP-lowering effects in line with the best existing therapies, with a favorable safety and tolerability profile at all doses tested. The trial was randomized, double-masked, placebo-controlled, and evaluated the efficacy, tolerability, safety, and pharmacokinetics of *trabodenoson* over two or four weeks of BID dosing with eye drops. Separate groups of patients received *trabodenoson* doses of 50, 100 or 200 mcg for two weeks, or 500 mcg for four weeks, and their IOP-lowering efficacy and safety data were compared to groups of patients dosed concurrently with placebo eye drops, also BID.

The primary efficacy endpoint was IOP (measured throughout the day). The primary efficacy analysis calculated the reduction in IOP from the patients' IOP at the beginning of the study (recorded before active drug was administered at the study 8 AM baseline). A second analysis calculated the reduction in IOP from a time-matched diurnal baseline. The IOP drop from baseline for each dose group (50, 100, 200 and 500 mcg) was then compared statistically to the IOP drop of a matched placebo group treated concurrently.

Results

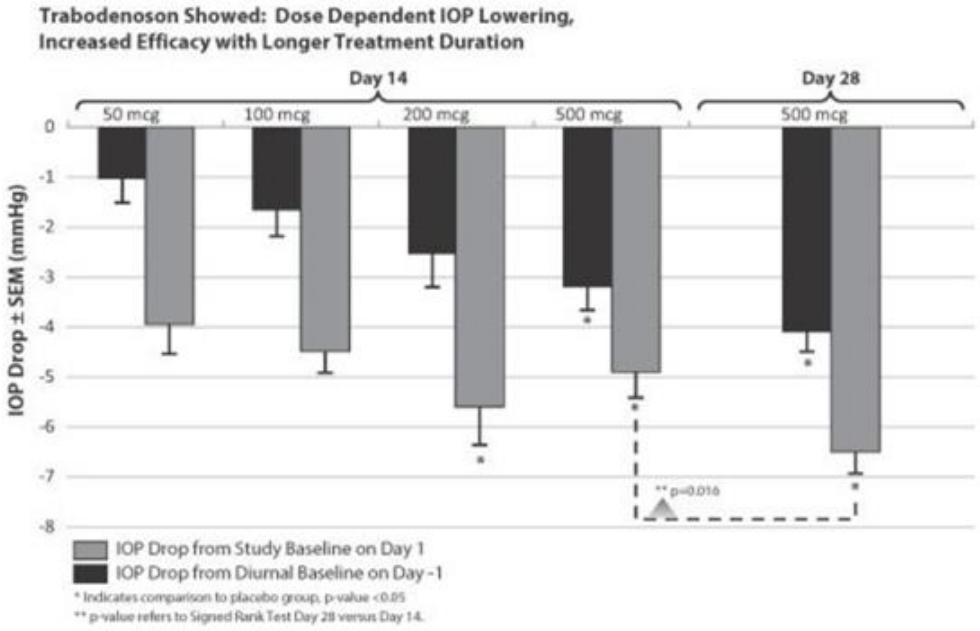
Patient Population: The characteristics of the patients in the dose groups were similar, including their ages, baseline IOPs, and diagnoses (OHT or POAG). The table below reflects information regarding the demographics of the patient populations that participated in the study, and shows that both diagnoses groups had similar baseline IOPs, and that groups treated with *trabodenoson* had characteristics that were similar to the placebo groups to which they were compared.

Baseline Demographics and IOP

		Trabodenoson Dose				
	Placebo	**50 mcg**	**100 mcg**	**200 mcg**	**500 mcg**	**Total Active**
Mean Age	59	56.6	55.6	53.8	57.6	56.3
n	59	17	17	17	34	85
Baseline IOP (mmHg)	26.6	26.1	25.6	26.1	26.2	26
OHT n(%)	22(37.3)	6(35.3)	8(47.1)	6(35.3)	14(41.2)	34(40.0)
Baseline IOP (mmHg)	26.7	27.2	25	27.1	26.3	26.3
POAG n(%)	37(62.7)	11(64.7)	9(52.9)	11(64.7)	20(58.8)	51(60.0)
Baseline IOP (mmHg)	26.5	25.5	26.1	25.5	26.1	25.9

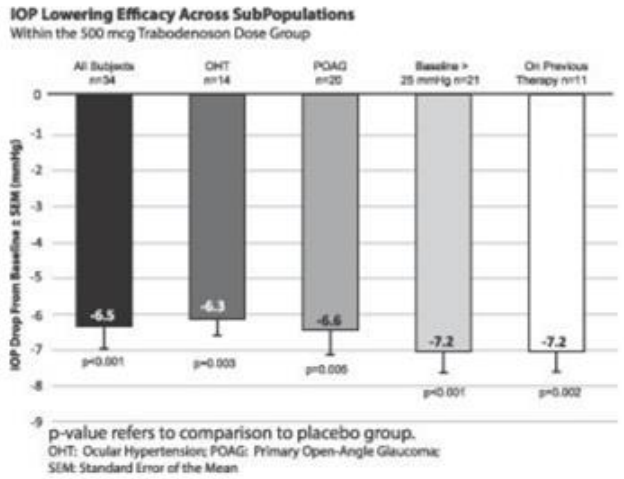
Efficacy

Both the 200 mcg dose and the 500 mcg doses at day 14, and the 500 mcg dose at day 28, met the primary endpoint demonstrating statistically significant improvements in IOP relative to the matched placebo ($p<0.05$ indicating a greater than 95% probability that the result was not a random event). Moreover, a clear increase in IOP-lowering efficacy was seen with increasing doses of *trabodenoson* (i.e. a dose response), and the most efficacious *trabodenoson* dose tested was the highest dose of 500 mcg. *Trabodenoson*'s primary efficacy endpoint (IOP drop from baseline) measured after four weeks of treatment (at day 28) had improved significantly from the same endpoint when measured after two weeks of treatment (at day 14). This improvement with additional treatment time was statistically significant ($p=0.016$). In the figure below, a clear trend for increasing IOP-lowering efficacy with increasing dose is evident. For the 500 mcg dose, the statistically significant increase in efficacy between day 14 and day 28 is illustrated on the right side of the figure.

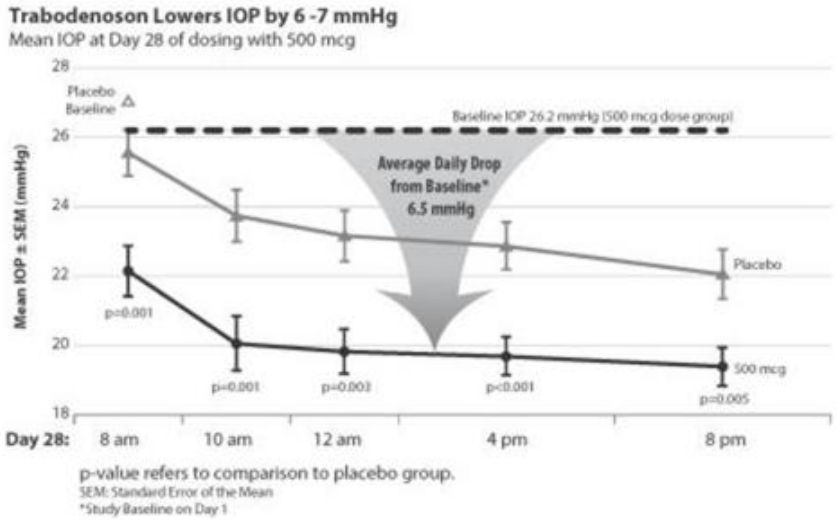


On average, doubling doses between 50 and 500 mcg increases IOP lowering from diurnal baseline by approximately 0.7 mmHg.

The IOP-lowering at the highest and most efficacious dose (500 mcg) was evaluated in various patient sub-populations to gain a sense of the ability to generalize the results over a diverse patient population. The figure below compares the IOP drop from study baseline (the primary endpoint analysis) for all patients (far left) to various sub-populations to the right of that. All of these patient subgroups responded to *trabodenoson*'s IOP-lowering effect.



When we rationally designed *trabodenoson*, our primary objective was to restore pressure regulation in eyes with high IOP, a risk factor for glaucoma. A healthy eye has a natural circadian rhythm that dictates a pattern of IOP over the day. We found that this pattern, or the shape of the IOP circadian rhythm curve throughout the day, is relatively unchanged by *trabodenoson* treatment, except that the overall IOP during the day is reduced by *trabodenoson* treatment as intended. We believe this indicates that the TM has been restored to an improved function resulting in a more normal average pressure, and that this normal daily IOP pattern indicates that the fundamental biology of pressure management in the eye has been preserved. The natural daily changes in IOP still exist, but at a significantly lower average pressure that we believe is less damaging to RGCs and the optic nerve. The figure below shows the primary efficacy parameter for the trial, IOP, at several timepoints throughout the day (diurnal IOP) for the highest dose tested and the placebo group at day 28.



Furthermore, after 28 days of BID dosing, the IOP-lowering effect persisted for an additional 24 hours after the last dose of medication, which we believe indicates the potential for *trabodenoson* monotherapy to be dosed QD.

Safety and Tolerability

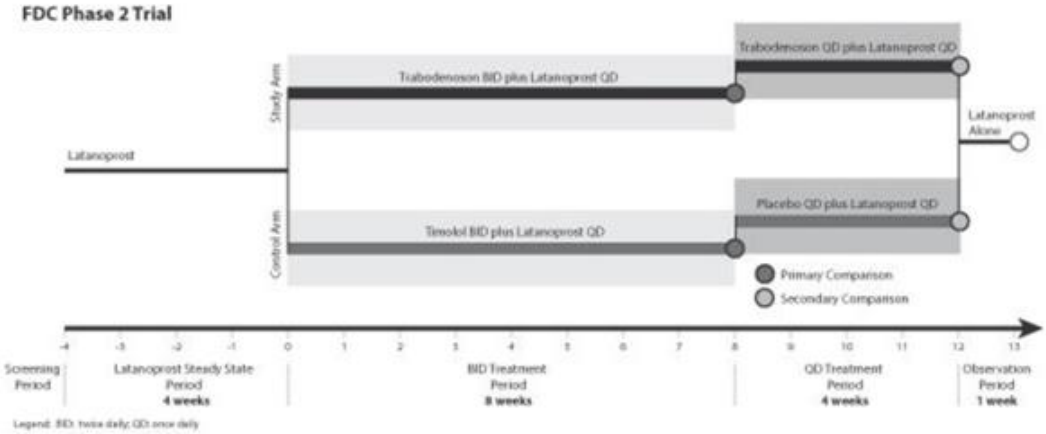
There were no SAEs or patients that withdrew due to safety findings that occurred once the drug was given. There were no signs of systemic safety issues in any of the non-ocular examinations, ECG evaluations or laboratory tests performed. Systemically, administration of *trabodenoson* eye drops was found to be well-tolerated. There were no changes noted from internal eye examinations or visual testing during drug treatment. The rate of conjunctival hyperemia in patients treated with *trabodenoson* was unchanged from the placebo run-in period (study baseline). There was no maximum tolerated dose determined because all doses tested were well-tolerated.

Trabodenoson Phase 2 Co-Administered with Latanoprost in Glaucoma Patients

In October 2014, we received top-line results from a Phase 2 trial in patients with POAG or OHT, in which *trabodenoson* eye drops were co-administered with *latanoprost* eye drops. The objective of the study was to evaluate the safety and additional IOP-lowering effect of *trabodenoson* when added either BID or QD to *latanoprost*. This trial enrolled 101 patients who had IOPs of greater than or equal to 24 mmHg despite one month of previous treatment with *latanoprost*. These patients are considered PGA poor-responders, as evidenced by persistently elevated IOP at levels that typically require the addition of a second drug to further lower IOP. The trial was randomized, double-masked, placebo- and active- controlled.

Following four weeks of *latanoprost* eye drops, otherwise healthy patients with an IOP greater than 24 mmHg and a diagnosis of either OHT or POAG were randomized for Part 1 of the study. In Part 1, the study arm consisted of BID-dosed *trabodenoson* (1.5%; 500 mcg nominal dose) plus *latanoprost* 0.005%, at the approved dose, QD. The control arm consisted of timolol 0.5%, an approved BID dose plus *latanoprost* 0.005% QD. Patients in both arms were treated for a total of eight weeks in Part 1 of the study to evaluate the additive effects of *trabodenoson* BID to *latanoprost* QD, with an active control consisting of timolol BID.

At the end of Part 1, after eight weeks of treatment, patients began Part 2 of the study. In Part 2, the study arm was switched to a QD dose of *trabodenoson* (3.0%, 1,000 mcg nominal dose) plus *latanoprost* 0.005% QD, and patients in the control arm were switched to placebo QD plus *latanoprost* 0.005% QD. Part 2 was designed to measure the additive effects of *trabodenoson* QD to *latanoprost* QD over an additional four weeks. The number of patients planned for enrollment was ~100 (50 patients per arm) for Part 1 and ~80 (40 patients per arm) for Part 2. This trial is outlined below.



The primary efficacy endpoint was IOP, measured throughout the day. The efficacy analyses calculated the reduction in IOP from the patients' IOP at study baseline and diurnal baseline (recorded after taking *latanoprost* for four weeks but before *trabodenoson* or *timolol* were added). In Part 1, these IOP drops from baseline, on *latanoprost*, were compared to the IOP drops of the control arm treated concurrently with *timolol*. In Part 2, the IOP drop from baseline in patients receiving *trabodenoson* QD plus *latanoprost* QD was compared to patients receiving placebo QD plus *latanoprost* QD.

Safety evaluations included recording of withdrawals or terminations and adverse events, or AEs. In each patient, both eyes were evaluated at regular intervals with internal eye exams (including pupil dilation with slit lamp examination of the inside of the eye) and external eye examinations (of the outside surface of the eye, eye lids and surrounding tissue). Visual function was also assessed. Overall health was assessed by physical exam, vital signs (including heart rate and blood pressure), electrocardiograms, or ECGs, for heart function and analysis of urine and blood samples (clinical chemistry). Plasma samples were collected to analyze the pharmacokinetic parameters, such as the half-life of any drug detected in the systemic circulation.

Results

Patient Population: The characteristics of the patients in the dose groups were similar, including their age, and baseline IOPs, which were not adequately controlled following a four-week run-in using *latanoprost* therapy. The table below includes information on the demographics of the patients that participated in the study.

Baseline Demographics and IOP

	Part 1		Part 2	
ITT population	***Trabodenoson*** **BID**	***Timolol*** **BID**	***Trabodenoson*** **QD**	***Placebo*** **QD**
n	50	51	37	43
Mean Age	62	61	63	61
Baseline IOP using *latanoprost* (mmHg)	25.71	25.86	25.68	25.86
OHT n (%)	23(46%)	13(25.5%)	15(40.5%)	12(28%)
Baseline IOP using *latanoprost* (mmHg)	25.78	25.65	25.93	25.29
POAG n (%)	27(54%)	38(74.5%)	22(59.5%)	31(72%)
Baseline IOP using *latanoprost* (mmHg)	25.65	25.93	25.50	26.08

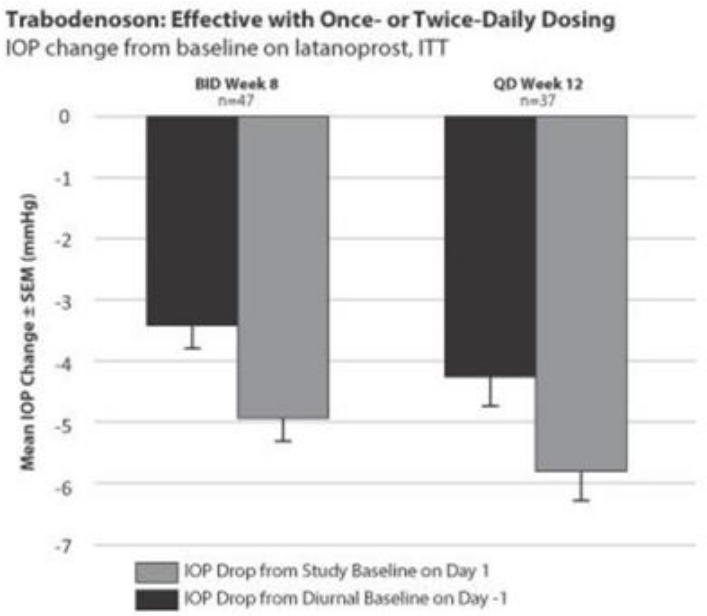
Discontinuations:

In Part 1, there were four discontinuations due to either protocol violations or exclusionary criteria (three patients were in the *trabodenoson* group and one was in the *timolol* group). In Part 2, there were two discontinuations; one was discontinued due to an AE and the other did not to return during follow-up, but provided no explanation (both were in the placebo group).

Efficacy

After eight weeks of BID dosing in Part 1, patients treated with *trabodenoson* co-administered with *latanoprost* experienced further mean reductions of IOP of 3.4 and 4.9 mmHg from diurnal and study baselines, respectively, beyond the IOP-lowering of *latanoprost*. After switching to QD *trabodenoson* in Part 2, and treating for an additional four weeks, QD dosing with *trabodenoson* resulted in a mean reduction in IOP of 4.3 and 5.8 mmHg from diurnal and study baseline, respectively, from the IOP on *latanoprost* alone. At the end of Part 2 (after 12 weeks), the IOP-lowering seen in the Study Eye (the eye treated with *trabodenoson*) was statistically significantly greater than the IOP drop of the patient's Control Eye (the patient's other eye that only received QD *latanoprost*).

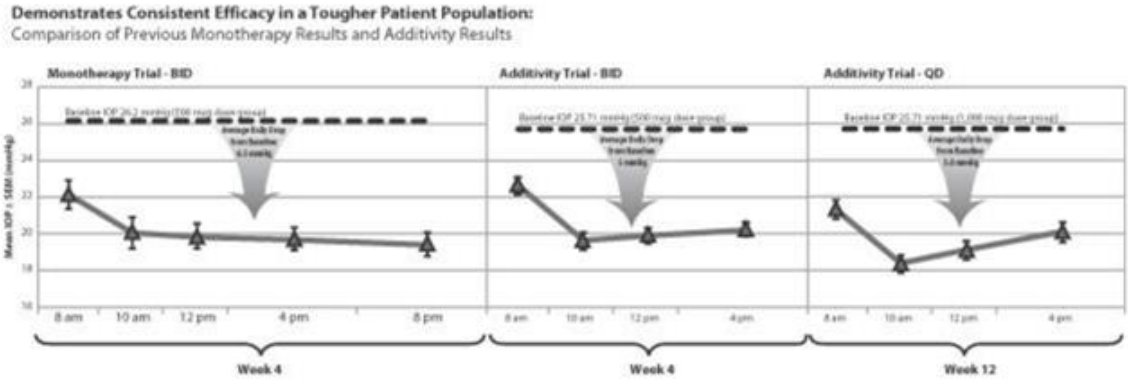
In Part 1 the IOP drop at the end of 8 weeks of treatment, in this population of *latanoprost* poor-responders, was less than *timolol* BID (0.5%) which dropped pressure 6.1 and 7.6 mmHg, on average from diurnal and study baselines, respectively.



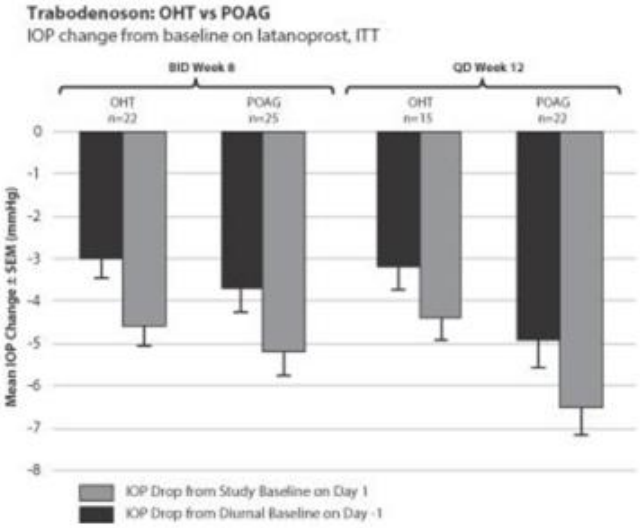
In Part 2 of the trial, QD *trabodenoson* lowered IOP an additional 4.3 and 5.8 mmHg from diurnal and study baseline, respectively, beyond the effect of *latanoprost* alone in this population of *latanoprost* poor-responders.

Consistency of Results across Phase II Studies

Mean reductions in IOP from study baseline ranging from 5.0 mmHg after four weeks of BID treatment to 5.8 mmHg after four weeks of QD treatment in the trial were similar to the 6.5 mmHg IOP reduction seen at the end of the four week *Trabodenoson Phase 2 Tolerability, Safety and Efficacy of Monotherapy in Glaucoma Patients* trial (the monotherapy trial). In the monotherapy trial, patients received only *trabodenoson*. The patients in the 2014 additivity trial represented a different patient population than those studied in the monotherapy trial. These patients had inadequate responses to *latanoprost*, as evidenced by persistently high IOP, despite *latanoprost* treatment for four weeks prior to randomization. This patient population typically requires the addition of a second drug to their PGA therapy to further lower IOP. Patients in the monotherapy trial, by contrast, were removed from all glaucoma medications, and thus represented a typical patient population studied in a Phase 3 glaucoma trial. Despite these differences in the patient populations, the efficacy of *trabodenoson* was consistent across trials, suggesting that *trabodenoson*'s mechanism of action is effective across a wide-range of glaucoma disease severity.



Both OHT and POAG patients responded to *trabodenoson* with POAG subjects showing the largest IOP drops.

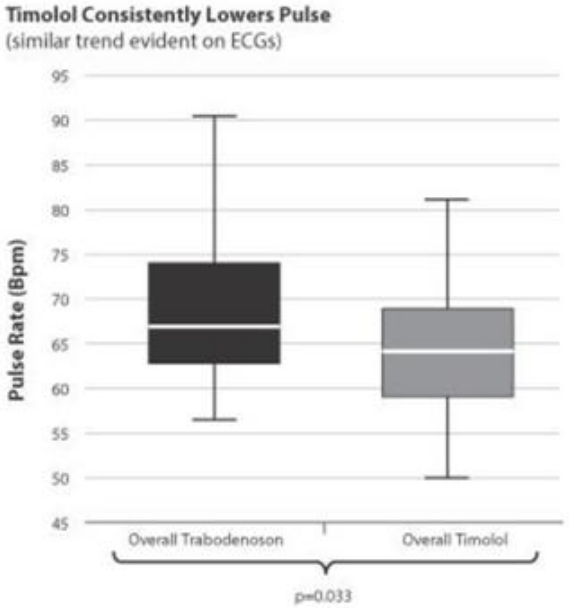


Safety and Tolerability

With the exception of a single patient who received placebo plus *latanoprost*, no patients dropped out of the trial as a result of a drug-related adverse effect or due to drug intolerability. *Trabodenoson* was well tolerated in the eye, with no drug related hyperemia detectable by ocular exam at four, eight or 12 weeks. Mild hyperemia seen on the first day of dosing in a minority of patients was back to baseline by the 10-week post dose ocular exams. *Trabodenoson* had no detectable systemic effects in any of the non-ocular examinations, ECG evaluations or laboratory tests performed. Overall AEs were similar in the BID phase (*Trabodenoson* 36%; *Timolol* 29%), with the *trabodenoson* rate dropping to 26% without the first-day hyperemias, and were also similar in the QD phase (*Trabodenoson* 16%; Placebo 14%) between treatment groups. However, *timolol* (dosed in one eye only) had systemic AEs associated with systemic beta blockade, including: dizziness, headache, fatigue and symptomatic sinus bradycardia.

Patients randomized to *timolol* also had lower pulse rates than in the *trabodenoson* group (the pulse rate was measured 30 minutes and one hour after dosing). This difference was statistically significant in the overall data (p=0.033) as well as at the individual timepoints (p=0.041 and p=0.030 at the 30 minute and one hour post-dose timepoints, respectively).

The pulse rates for both groups are shown in the boxplot below, which includes the minimum and maximum values, median (white line), and the boundaries of the upper and lower quartiles (top and bottom of the box).



Trabodenoson Repeat-Dose Safety and Tolerability in Adult Healthy Volunteers

We conducted a randomized, double-masked, placebo-controlled, dose-escalation trial in healthy volunteers, aged 35-65, with the primary objective of characterizing the safety and tolerability profile of *trabodenoson* and identifying a maximum tolerated dose (a dose that was associated with limiting or intolerable side effects).

Ten subjects were assigned to each of seven consecutive cohorts (six to active *trabodenoson* and four to matched placebo). Cohorts 1 through 6 consisted of sequential, escalating doses (200, 400, 800, 1600, 2400 and 3200 mcg of *trabodenoson*) which were given topically to a single eye, BID, for 14 days. The 3200 mcg dose was the highest dose that could be administered to a single eye at one time due to, among others, the limitations of the formulation. Cohort 7 included eight step-wise escalating doses of *trabodenoson*, given in both eyes. Doses given to this cohort ranged from 200-3200 mcg in a single eye and totaled 1800-6400 mcg for both eyes combined. Dose escalation to the next dose level proceeded only after masked review of the safety data from the preceding dose level.

Systemic safety assessments included: AEs, other medications used, physical examinations, vital signs, clinical laboratory tests of blood and urine samples, extensive monitoring of cardiac function and health (12-lead ECG tracings, continuous cardiac monitoring and cardiac troponin concentrations), lung function testing (FEV_1), sleep (Karolinska Sleepiness Scale), kidney function and withdrawals or terminations. No systemic safety signals were found at any of the doses tested.

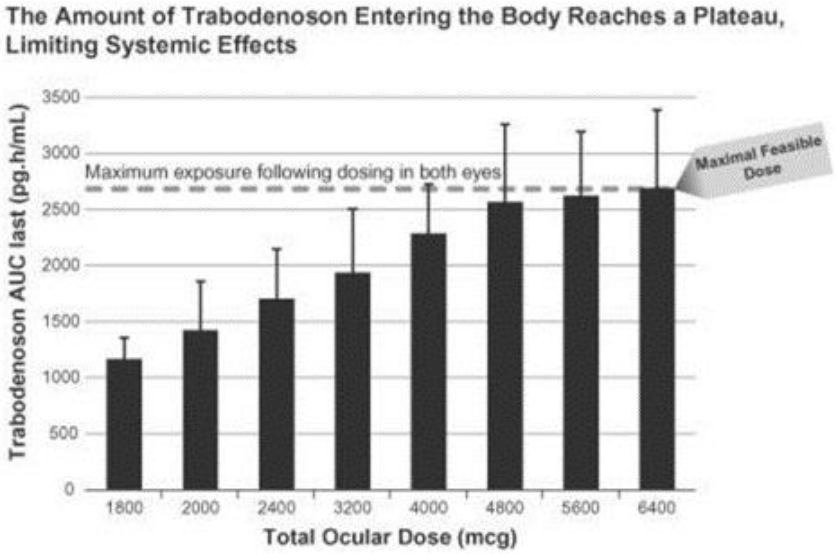
Ocular safety assessments included vision tests (visual acuity), IOP measurements, as well as internal and external eye examinations. No significant changes were seen in IOP measurements and examination of the periorbital area, eyelids, eyelashes, pupils, cornea, iris and sclera. The only ocular finding was short-lived, self-limited conjunctival hyperemia that was dose-related, usually mild in severity, decreased with continuing exposure, and was not accompanied by evidence that it was related to inflammation, such as persistent anterior chamber cells or flare. The incidence of clinically significant eye redness reported as an AE was extremely low (1 of 42) in subjects randomized to *trabodenoson*.

Early Terminations and Withdrawals

Three subjects randomized to placebo were terminated early from the study for reasons unrelated to the study drug. Only one subject assigned to active study drug was withdrawn. The study subject's laboratory tests revealed findings consistent with gallbladder disease (chronic cholecystitis), so the subject was withdrawn from the clinical trial (without unmasking the subject's treatment assignment) and referred for a surgical consult resulting in the subject having chronic gallbladder stones removed.

Pharmacokinetic Data

The pharmacokinetics data indicated that the exposure to *trabodenoson* generally increased in a dose-dependent manner. At the highest three doses, there were no apparent increases in systemic exposure with increasing dose. This plateau effect suggests that little additional drug is absorbed into systemic circulation following doses above 4800 mcg (2400 mcg per eye), as reflected in the figure below.



Conclusions

In conclusion, no safety or tolerability issues were identified in either the eye or the body as a whole. Due to the lack of clinically significant findings following in depth safety testing for systemic and ocular effects of *trabodenoson*, no maximum tolerated dose could be identified. Systemic exposure to *trabodenoson* appeared to be limited above ocular doses totaling 4800 mcg, indicating an apparent limitation to the amount of drug that can be delivered to the body by dosing in the eye.

Trabodenoson Monotherapy Tolerability, Safety and Efficacy

We conducted a Phase 1/2 multi-center, randomized, double-masked, placebo-controlled, dose-escalation trial in 70 adults with POAG and OHT with the primary objective of characterizing the safety and tolerability of increasing doses of a pilot formulation of *trabodenoson* monotherapy.

Subjects were sequentially assigned to one of seven consecutive cohorts (eight to active *trabodenoson* and four to matched placebo); consisting of sequential, escalating single-doses of 2.5, 7.5, 20, 60, 180, 350 or 700 mcg of *trabodenoson* given topically to a single study eye.

Efficacy (IOP-lowering), tolerability, safety and pharmacokinetics assessments were performed following study drug administration, and dose escalation from one cohort to the next cohort proceeded only after masked review of the safety data from the preceding cohort.

Conclusions

In conclusion, *trabodenoson* monotherapy ophthalmic solution up to and including 700 mcg were well-tolerated. This preliminary formulation of *trabodenoson* demonstrated activity at lowering IOP following single doses of 350 mcg and 700 mcg in patients with POAG or OHT.

Development Strategy

Trabodenoson

We had an End-of-Phase 2 meeting with the FDA in 2015 to discuss our Phase 3 program for *trabodenoson* monotherapy and to confirm the design and endpoints for the Phase 3 pivotal trials. At the meeting, we reached agreement on the design of our initial Phase 3 study, as well as the overall regulatory path for *trabodenoson*. We commenced our Phase 3 program for *trabodenoson* monotherapy in October 2015 and reported top-line results in January 2017. The recently completed Phase 3 pivotal trial, MATrX-1, did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute IOP from placebo at every single one of the 12 time points comprising the primary endpoint. This was due to a larger than expected treatment effect in the placebo/vehicle group, as compared to both our prior Phase 2 data and a recent meta-analysis examining placebo responses from 10 placebo-controlled trials, which showed a placebo/vehicle result of -2.01 mmHg (Raber, et al). During analysis of the IOP data from the trial, a treatment-by-site interaction was found where a small number of sites (4 sites out of a total of 55) caused an important change in the expected vehicle results. The review of the MATrX-1 data is ongoing and upon completion of all analyses, we plan to request a meeting with the FDA in the first half of 2017 to discuss these findings.

The overall program will encompass a total subject exposure to *trabodenoson* of at least 1,300 patients. The final design of the second Phase 3 trial will be impacted by the findings of the initial Phase 3 trial. Following a run-in period, the second Phase 3 trial is expected to run for at least 12 weeks of active treatment with the primary endpoint of IOP-lowering over the day.

The initial Phase 3 trial was a three-month study with five treatment arms, for a total of approximately 300 patients with 3 *trabodenoson* treatment arms. The *trabodenoson* doses evaluated were 1,000 mcg QD, 2,000 mcg QD, and 1,500 mcg BID. The trial investigated both once-daily (QD) and twice-daily (BID) dosing, as some patients may benefit from a twice daily dosing regimen. The primary efficacy endpoint of the study was IOP, measured at four time points during the day after 4, 6 and 12 weeks of treatment. The IOP of the *trabodenoson* treated subjects was statistically compared to those of placebo treated subjects. A timolol arm was included for study validation, but not for statistical comparison.

The FDA requires that a total of at least 1,300 patients be exposed to at least a single dose of *trabodenoson*, and the complete submission package must also contain safety data from at least 300 patients treated with *trabodenoson* for at least six months, and at least 100 patients treated for at least a year. These longer-term treatments will be accomplished in a long-term safety trial conducted at the highest anticipated *trabodenoson* dose. If the primary objectives of all trials in our Phase 3 program are met, we plan to submit an NDA to the FDA for marketing approval of *trabodenoson* for the treatment of glaucoma in the United States.

Fixed-Dose Combination of Trabodenoson and Latanoprost

We are also developing an FDC of *trabodenoson* and *latanoprost*. We have not filed a separate investigational new drug application, or IND, for the FDC, as we expect to be able to rely on the existing *trabodenoson* IND. Similarly, we have not conducted a Phase 1 trial for the FDC as we were able to rely on the safety and tolerability data generated in our completed trials for *trabodenoson* as a monotherapy.

The results of the Phase 2 trial that evaluated the efficacy and safety of the combination of *latanoprost* and *trabodenoson*, at two dose levels, and when given QD and BID, informed the design and format of the currently ongoing study which was structured to evaluate the safety and efficacy of various dose combinations and dosing patterns of an FDC of *latanoprost* and *trabodenoson*. The commencement of our Phase 2 program for the FDC product candidate as well as future FDC trials will depend on successful cGMP manufacturing of stable FDC dosage forms. We initiated our Phase 2 program in 2016 and plan to start our Phase 3 FDC program in 2018. We expect our FDC product candidate to benefit many patients with higher IOPs and more severe disease that typically require more aggressive medical treatment. For this reason, the patient population for the FDC program is expected to carry a higher disease burden. As with the monotherapy product development, the FDA requirements for long-term dosing data (at least 300 patients treated with the FDC for at least six months, and at least 100 patients treated for at least a year) will require the program to include a long-term safety study.

Neuroprotection and Degenerative Retinal Diseases

We plan to study the neuroprotective potential of *trabodenoson* monotherapy and our FDC product candidate to slow the loss of vision significantly more than attributable to IOP-lowering alone either in glaucoma patients or other rarer forms of optic neuropathy. While supported by the basic biology of adenosine, we have not yet conducted a formal program of studies to prove neuroprotection and have not filed an IND related to this program. This evaluation may include longer longitudinal studies in glaucoma patients, as potentially smaller patient groups with rapidly-progressing optic nerve damage. Although treatment times will be measured in years rather than months, this effort can run in parallel to the normal development trials, or may be included in the objectives of the planned long-term safety trials. The regulatory path for such an indication is thus far uncharted, so significant regulatory as well as clinical risk

is anticipated for such a program and close interaction with regulatory agencies will be required. Due to the speculative nature of the development, it is difficult at this time to predict if or when an NDA submission in support of neuroprotection indication may be submitted. We plan to continue pre-clinical and proof-of-concept trials for optic neuropathies and degenerative retinal diseases in 2017.

Competition

The pharmaceutical industry is characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our experience and scientific knowledge provide us with competitive advantages, we face competition from established branded and generic pharmaceutical companies, such as Novartis International AG and its subsidiary Alcon Labs, Pfizer/Allergan Inc., Bausch + Lomb, Inc. (now a unit of Valeant Pharmaceuticals International, Inc.), Merck & Co., Inc., Santen Inc., Aerie Pharmaceuticals, Inc. and smaller biotechnology and pharmaceutical companies, as well as from academic institutions, government agencies and private and public research institutions, which may in the future develop products to treat glaucoma. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that the key competitive factors affecting the success of our product candidates, if approved, are likely to be efficacy, safety, convenience, price, tolerability and the availability of coverage and adequate reimbursement from governmental authorities and other third-party payors.

Many of our 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. Glaukos Corporation recently commercialized a trabecular micro-bypass stent that is implanted in the eye during cataract surgery and allows fluid to flow from the anterior of the eye into the collecting channels, bypassing the TM. In addition, early-stage companies that are also developing glaucoma treatments, such as Aerie Pharmaceuticals, Inc., which is developing a Rho kinase/norepinephrine transport inhibitor, may prove to be significant competitors. We expect that our competitors will continue to develop new glaucoma treatments, which may include eye drops, oral treatments, surgical procedures, implantable devices or laser treatments.

Other early-stage companies may also compete through collaborative arrangements with large and established companies. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer adverse effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours. In addition, our ability to compete may be affected because in many cases physicians, insurers or other third-party payors may encourage the use of generic products. The market for glaucoma prescriptions is highly competitive and is currently dominated by generic drugs, such as *latanoprost* and timolol, and additional products are expected to become available on a generic basis over the coming years. If any of our product candidates are approved, we expect that they will be priced at a premium over competitive generic products and consistent with other branded glaucoma drugs.

Manufacturing

Trabodenoson is a small molecule that is capable of being manufactured in reliable and reproducible synthetic processes from readily available starting materials. We believe the chemistry used to manufacture *trabodenoson* is amenable to a scale up and does not require unusual equipment in the manufacturing process. We do not currently operate manufacturing facilities for clinical or commercial production of our product candidates. We currently rely on third-party manufacturers to produce the active pharmaceutical ingredient and final drug product for our clinical trials. We manage such production with all our vendors on a purchase order basis in accordance with applicable master service and supply agreements. We do not have long-term agreements with these manufacturers or any other third-party suppliers. *Latanoprost* and timolol, used in our clinical trials, are available in commercial quantities from multiple reputable third-party manufacturers. We intend to procure quantities on a purchase order basis for our clinical and commercial production. If any of our existing third-party suppliers should become unavailable to us for any reason, we believe that there are a number of potential replacements, although we might experience a delay in our ability to obtain alternative suppliers. We also do not have any current contractual relationships for the manufacture of commercial supplies of our product candidates if they are approved. With respect to commercial production of our product candidates in the future, we plan to outsource production of the active pharmaceutical ingredients and final drug product manufacturing if they are approved for marketing by the applicable regulatory authorities.

We expect to continue to develop drug candidates that can be produced in a cost effective manner at contract manufacturing facilities. However, should a supplier or manufacturer on which we have relied to produce a product candidate provide us with a faulty product or such product is later recalled, we would likely experience delays and additional costs, each of which could be significant.

Intellectual Property

Our success depends in part on our ability to obtain and maintain proprietary protection for our products and 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 own a patent portfolio covering the *trabodenoson* compound that includes issued patents in the United States, Europe, Japan, and several other countries. These composition-of-matter patents are scheduled to expire by early 2026 in the United States and by mid-2025 abroad. We also own an issued U.S. patent and have pending patent applications in Europe and Japan relating to the use of *trabodenoson* for reducing IOP. The issued U.S. patent is scheduled to expire in 2031 and the pending foreign patent applications, if issued, are scheduled to expire by 2030. In 2016, we had a U.S. composition-of-matter patent issued that covers polymorphs of *trabodenoson*. This patent is scheduled to expire in 2033. A detailed freedom-to-operate analysis has been conducted and we are not aware of any third party rights or impediments to commercializing *trabodenoson* for use in ophthalmic indications in the United States or Europe.

Our patent portfolio includes issued U.S. patents relating to combinations of *trabodenoson* with carbonic anhydrase inhibitors, beta blockers and prostaglandins (PGAs). These U.S. patents are scheduled to expire in 2031 and 2032. At the end of 2016, we also had an ophthalmic formulation patent issue in the U.S. that covers our current ophthalmic formulation. This U.S. patent is scheduled to expire in 2034.

We are also pursuing additional patent applications in the United States and abroad relating to:

- combinations of *trabodenoson* with PGAs, carbonic anhydrase inhibitors or beta blockers, in patent applications which, if issued, are scheduled to expire by 2031;
- polymorphs of *trabodenoson*, in patent applications which, if issued, are scheduled to expire by 2033;
- formulations of *trabodenoson*, in patent applications which, if issued, are scheduled to expire by 2034; and
- ocular neuroprotective uses of *trabodenoson*, in patent applications which, if issued, are scheduled to expire by 2034.

As we advance the development of our *trabodenoson* products and clinical development we continue to look at opportunities to file additional patent applications covering new and innovative developments to ensure we have a patent portfolio that is multifaceted. For such additional applications, we will continue to seek patent protection in the United States and other jurisdictions that are important in the ophthalmic markets.

In addition to our patents and patent applications, we keep certain of our proprietary information as trade secrets, which we seek to protect by confidentiality agreements with our employees and third parties, and by seeking to maintain the physical security of our premises and physical and electronic security of our information technology systems.

Government Regulation

FDA Regulation and Marketing Approval

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and related regulations. Drugs are also subject to other federal, state and local statutes and regulations. Failure to comply with the applicable United States regulatory requirements at any time during the product development process, approval process or after approval may subject an applicant to administrative or judicial sanctions and non-approval of product candidates. These sanctions could include, among other things, the imposition by the FDA or an Institutional Review Board, or IRB, of a clinical hold on trials, the FDA's refusal to approve pending applications or related supplements, withdrawal of an approval, untitled or warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, restitution, disgorgement, civil penalties or criminal prosecution. Such actions by government agencies could also require us to expend a large amount of resources to respond to the actions. Any agency or judicial enforcement action could have a material adverse effect on us.

The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, approval, manufacture, distribution and marketing of pharmaceutical products. These agencies and other federal, state and local entities regulate research and development activities and the testing, manufacture, quality control, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, post-approval monitoring,

advertising, promotion, sampling and import and export of our products. Our drugs must be approved by the FDA through the NDA process before they may be legally marketed in the United States. See “The NDA Approval Process” below.

The process required by the FDA before drugs may be marketed in the United States generally involves the following:

- completion of non-clinical laboratory tests, animal studies and formulation studies conducted according to Good Laboratory Practices, or GLP, or other applicable regulations;
- submission of an IND, which allows clinical trials to begin unless FDA objects within 30 days;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug for its intended use or uses conducted in accordance with FDA regulations and Good Clinical Practices, or GCP, which are international ethical and scientific quality standards meant to ensure that the rights, safety and well-being of trial participants are protected and that the integrity of the data is maintained;
- preparation and submission to the FDA of an NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of pre-approval inspection of manufacturing facilities and clinical trial sites at which the product, or components thereof, are produced to assess compliance with cGMP requirements and of selected clinical trial sites to assess compliance with GCP requirements; and
- FDA approval of an NDA which must occur before a drug can be marketed or sold.

Preclinical Studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as in vitro and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The 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 drug and finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

IND and Clinical Trials

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Prior to commencing the first clinical trial, an initial IND, which contains the results of preclinical testing along with other information, such as information about product chemistry, manufacturing and controls and a proposed protocol, must be submitted to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA unless the FDA within the 30-day time period raises concerns or questions about the drug product or the conduct of the clinical trial and imposes a clinical hold. A clinical hold may also be imposed at any time while the IND is in effect. In such a case, the IND sponsor must resolve any outstanding concerns with the FDA before the clinical trial may begin or re-commence. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence or continue.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA or IND so long as the clinical trial is conducted in compliance with GCP, and the FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

A separate submission to the existing IND must be made for each successive clinical trial to be conducted during product development. Further, an independent IRB for each site at which the clinical trial will be conducted must review and approve the clinical trial before it commences at that site. Informed written consent must also be obtained from each trial subject. Regulatory

authorities, including the FDA, an IRB, a data safety monitoring board or the sponsor, may suspend or terminate a clinical trial at any time on various grounds, including a finding that the participants are being exposed to an unacceptable health risk or that the clinical trial is not being conducted in accordance with FDA requirements.

For purposes of NDA approval, human clinical trials are typically conducted in sequential phases that may overlap:

- Phase 1– the drug is initially given to healthy human subjects or patients and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion. These trials may also provide early evidence on effectiveness. During Phase 1 clinical trials, sufficient information about the investigational drug's pharmacokinetics and pharmacologic effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.
- Phase 2– trials are conducted in a limited number of patients in the target population to identify possible adverse effects and safety risks, to determine the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- Phase 3– when Phase 2 evaluations demonstrate that a dosage range of the product appears effective and has an acceptable safety profile, and provide sufficient information for the design of Phase 3 trials, Phase 3 trials are undertaken to provide statistically significant evidence of clinical efficacy and to further test for safety in an expanded patient population at multiple clinical trial sites. They are intended to further evaluate dosage, effectiveness and safety, to establish the overall benefit-risk relationship of the investigational drug and to provide an adequate basis for product labeling and approval by the FDA. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug.

All clinical trials must be conducted in accordance with FDA regulations, GCP requirements and their protocols in order for the data to be considered reliable for regulatory purposes. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all.

An investigational drug product that is a combination of two different drugs in a single dosage form must comply with an additional rule that requires that each component make a contribution to the claimed effects of the drug product and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling of the drug product. This typically requires larger studies that test the drug against each of its components. In addition, typically, if a drug product is intended to treat a chronic disease, as is the case with our products, safety and efficacy data must be gathered over an extended period of time, which can range from six months to three years or more.

Government regulation may delay or prevent marketing of product candidates or new drugs for a considerable period of time and impose costly procedures upon our activities.

Disclosure of Clinical Trial Information

Sponsors of clinical trials of FDA-regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved up to a maximum of two years. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

The NDA Approval Process

In order to obtain approval to market a drug in the United States, a marketing application must be submitted to the FDA that provides data establishing to the FDA's satisfaction the safety and effectiveness of the investigational drug for the proposed indication. Each NDA submission requires a substantial user fee payment unless a waiver or exemption applies. The application includes all relevant data available from pertinent non-clinical or preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators that meet GCP requirements.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to submission of an IND, at the End-of-Phase 1 or 2, and before an NDA is submitted. Meetings at other times may be

requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice and for the sponsor and the FDA to reach agreement on the next phase of development. Sponsors typically use the End-of-Phase 2 meetings to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 trials that they believe will support approval of the new drug.

The results of product development, non-clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. It may request additional information rather than accept a NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. The FDA has 60 days from its receipt of an NDA to conduct an initial review to determine whether the application will be accepted for filing based on the agency's threshold determination that the application is sufficiently complete to permit substantive review. If the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. The FDA has agreed to specific performance goals on the review of NDAs and seeks to review standard NDAs for new molecular entities in 10 months from the 60-day filing date (typically 12 months from submission of the NDA). The review process may be extended by the FDA for three additional months to consider certain late-submitted information or information intended to clarify information already provided in the submission. After the FDA completes its substantive review of an NDA, it will communicate to the sponsor that the drug will either be approved, or it will issue a complete response letter to communicate that the NDA will not be approved in its current form and inform the sponsor of changes that must be made or additional clinical, non-clinical or manufacturing data that must be received before the application can be approved, with no implication regarding the ultimate approvability of the application or the timing of any such approval, if ever. If or when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA may issue an approval letter. FDA has committed to reviewing such resubmissions in two to six months depending on the type of information included. The FDA may refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and, if so, under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA may inspect one or more clinical sites to assure compliance with GCP. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it typically will outline the deficiencies and often will request additional testing or information. This may significantly delay further review of the application. If the FDA finds that a clinical site did not conduct the clinical trial in accordance with GCP, the FDA may determine the data generated by the clinical site should be excluded from the primary efficacy analyses provided in the NDA. Additionally, notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

The FDA may require, or companies may pursue, additional clinical trials after a product is approved. These so-called Phase 4 trials may be made a condition to be satisfied for continuing drug approval. The results of Phase 4 trials can confirm the effectiveness of a product candidate and can provide important safety information. In addition, the FDA has authority to require sponsors to conduct post-marketing trials to specifically address safety issues identified by the agency. See "Post-Marketing Requirements" below.

The FDA also has authority to require a Risk Evaluation and Mitigation Strategy, or a REMS, from manufacturers to ensure that the benefits of a drug outweigh its risks. A sponsor may also voluntarily propose a REMS as part of the NDA submission. The need for a REMS is determined as part of the review of the NDA. Based on statutory standards, elements of a REMS may include "Dear Doctor letters," a medication guide, more elaborate targeted educational programs, and in some cases distribution and use restrictions, referred to as "elements to assure safe use," or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. These elements are negotiated as part of the NDA approval, and in some cases the approval date may be delayed. Once adopted, REMS are subject to periodic assessment and modification.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Even if a product candidate receives regulatory approval, the approval may be limited to specific disease states, patient populations and dosages, or might contain significant limitations on use in the form of warnings, precautions or contraindications, or in the form of onerous risk management plans, restrictions on distribution or use, or post-marketing trial requirements. Further, even after regulatory approval is obtained, later discovery of previously unknown problems with a product may result in restrictions on the product,

including safety labeling or imposition of a REMS, the requirement to conduct post-market studies or clinical trials or even complete withdrawal of the product from the market. Delay in obtaining, or failure to obtain, regulatory approval for our products, or obtaining approval but for significantly limited use, would harm our business. In addition, we cannot predict what adverse governmental regulations may arise from future United States or foreign governmental action.

The Hatch-Waxman Amendments

Under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, a portion of a product's U.S. patent term that was lost during clinical development and regulatory review by the FDA may be restored by returning up to five years of patent life for a patent that covers a new product or its use. This period is generally one-half the time between the effective date of an IND (falling after issuance of the patent) and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application, provided the sponsor acted with diligence. Patent term restorations, however, cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended and the extension must be applied for prior to expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Market Exclusivity

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain competing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an Abbreviated New Drug Application, or ANDA, or a 505(b)(2) NDA submitted by another company for a drug product that contains the protected active moiety. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, or supplement, for example, for new indications, dosages or strengths of an existing drug. During the exclusivity period, the FDA may not approve an ANDA or 505(b)(2) application for the same conditions of approval as the innovator drug. This three-year exclusivity protects only the conditions of approval associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs or 505(b)(2) applications with different conditions of approval. For example, if three-year exclusivity protected a new extended-release dosage form, the exclusivity would not block approval of an ANDA or 505(b)(2) application for the original immediate-release version of the drug. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the non-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent exclusivity. 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.

Post-Marketing Requirements

Following approval of a new product, a pharmaceutical company and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse experiences with the product, providing the regulatory authorities with updated safety and efficacy information, product sampling and distribution requirements, and complying with promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling, or off-label use, limitations on industry-sponsored scientific and educational activities and requirements for promotional activities involving the internet. Although physicians may, in their independent professional medical judgment, prescribe legally available drugs for off-label uses, manufacturers typically may not market or promote such off-label uses. Modifications or enhancements to the product or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, who may or may not grant approval or may include a lengthy review process.

Prescription drug advertising is subject to federal, state and foreign regulations. In the United States, the FDA regulates prescription drug promotion, including direct-to-consumer advertising. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Any distribution of prescription drug products and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the FDCA.

In the United States, once a product is approved, its manufacturing is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such product or may result in restrictions on a product, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the product from the market.

In addition, the manufacturer and/or sponsor under an approved NDA are subject to annual product and establishment fees. These fees are typically increased annually.

The FDA also may require post-marketing testing, also known as Phase 4 testing, to monitor the effects of an approved product or place conditions on an approval via a REMS that could restrict the distribution or use of the product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, untitled or warning letters from the FDA, mandated corrective advertising or communications with doctors, withdrawal of approval, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Coverage and Reimbursement

Sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payors, including government healthcare program administrative authorities, managed care organizations, private health insurers, and other entities. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all of part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Therefore, our products, once approved, may not obtain market acceptance unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products.

The process for determining whether a third-party payor will provide coverage for a drug product typically is separate from the process for setting the price of a drug product or for establishing the reimbursement rate that the payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the FDA-approved drugs for a particular indication. A decision by a third-party payor not to cover our product candidates could reduce physician utilization of our products once approved. Moreover, a third-party payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. Additionally, coverage and reimbursement for drug products can differ significantly from payor to payor. One third-party payor's decision to cover a particular drug product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor separately and will be a time-consuming process.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for drug products and medical services, examining the medical necessity and reviewing the cost effectiveness of drug products and medical services, in addition to questioning safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after FDA approval or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit.

In particular, our success may depend on our ability to obtain coverage and adequate reimbursement through Medicare Part D plans for our products that obtain regulatory approval. The Medicare Part D program provides a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Parts A and B, Part D coverage is not standardized. In general, Part D prescription drug plan sponsors have flexibility regarding coverage of Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class, with certain exceptions. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutics committee. Government payment for some of the costs of prescription drugs may increase demand for products for which we receive regulatory approval. However, any negotiated prices for our future products covered by a Part D prescription drug plan will likely be discounted, thereby lowering the net price realized on our sales to pharmacies. Moreover, while the Part D program applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-government payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the U.S. Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our product candidates, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor’s product could adversely affect the sales of our product candidates, once approved. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the European Union do not follow price structures of the United States and generally tend to be significantly lower.

Anti-Kickback and False Claims Laws and Other Regulatory Matters

In the United States, among other things, the research, manufacturing, distribution, sale and promotion of drug products and medical devices are potentially subject to regulation and enforcement by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare & Medicaid Services, other divisions of the United States Department of Health and Human Services (e.g., the Office of Inspector General), the Drug Enforcement Administration, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency, state Attorneys General and other state and local government agencies. Our current and future business activities, including for example, sales, marketing and scientific/educational grant programs must comply with healthcare regulatory laws, as applicable, which may include the Federal Anti-Kickback Statute, the Federal False Claims Act, as amended, the privacy and security regulations promulgated under the Health Insurance Portability and Accountability Act, or HIPAA, as amended, physician payment transparency laws, and similar state laws. Pricing and rebate programs must comply with the Medicaid Drug Rebate Program requirements of the Omnibus Budget Reconciliation Act of 1990, as amended, and the Veterans Health Care Act of 1992, as amended. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. All of these activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The Federal Anti-Kickback Statute makes it illegal for any person or entity, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully, directly or indirectly, in cash or in kind, solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchasing, leasing, ordering or arranging for or

recommending the purchase, lease or order of, any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as Medicare or Medicaid. The term "remuneration" has been broadly interpreted to include anything of value. The Federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Additionally, the intent standard under the Federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care Education and Reconciliation Act, or collectively the ACA, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the Federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the Federal False Claims Act. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, many states have adopted laws similar to the Federal Anti-Kickback Statute. Some of these state prohibitions apply to the referral of patients for healthcare services reimbursed by any insurer, not just federal healthcare programs such as Medicare and Medicaid. Due to the breadth of these federal and state anti-kickback laws, and the potential for additional legal or regulatory change in this area, it is possible that our future business activities, including our sales and marketing practices and/or our future relationships with ophthalmologists and optometrists might be challenged under anti-kickback laws, which could harm us.

Federal false claims and false statement laws, including the civil False Claims Act, prohibits any person or entity from, among other things, knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent. This statute has been interpreted to prohibit presenting claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. For example, pharmaceutical companies have been found liable under the Federal Civil False Claims Act in connection with their off-label promotion of drugs. Penalties for a civil False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between $5,500 and $11,000 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the Federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. If the government were to allege that we were, or convict us of, violating these false claims laws, we could be subject to a substantial fine and may suffer a decline in our stock price. In addition, private individuals have the ability to bring actions under the Federal Civil False Claims Act and certain states have enacted laws modeled after the Federal False Claims Act.

Additionally, HIPAA created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

There are also an increasing number of state laws that require manufacturers to make reports to states on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. In addition, as discussed below, a similar federal requirement under the Physician Payments Sunshine Act, requires certain manufacturers to track and report to the federal government certain payments provided to physicians and teaching hospitals made in the previous calendar year, as well as certain ownership and investment interests held by physicians and their immediate family members. These laws may affect our sales, marketing and other promotional activities by imposing administrative and compliance burdens on us. In addition, given the lack of clarity with respect to these laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state and federal authorities.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final Omnibus Rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information on certain types of individuals and organizations. In addition, certain state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other and from HIPAA in significant ways and may not have the same effect, thus complicating compliance efforts.

The failure to comply with regulatory requirements subjects us to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in significant criminal, civil and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in federal healthcare programs, such as Medicare and Medicaid, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, refusal to allow us to enter into supply contracts, including government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, 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.

We plan to develop a comprehensive compliance program that establishes internal controls to facilitate adherence to the law and program requirements to which we will or may become subject because we intend to commercialize products that could be reimbursed under a federal healthcare program and other governmental healthcare programs.

Changes in law or the interpretation of existing law could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

Affordable Care Act and Other Reform Initiatives

In the United States and some foreign jurisdictions, there have been, and likely will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system directed at broadening the availability of healthcare and containing or lowering the cost of healthcare.

By way of example, in March 2010, the ACA was enacted. The ACA includes measures that have or will significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA of greatest importance to the pharmaceutical industry are the following:

- The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the U.S. Department of Health and Human Services in exchange for state Medicaid coverage of most of the manufacturer's drugs. ACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic agents to 23.1% of average manufacturer price, or AMP, and adding a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP.
- The ACA expanded the types of entities eligible to receive discounted 340B pricing, although, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs used in orphan indications. In addition, because 340B pricing is determined based on AMP and Medicaid drug rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discounts to increase. The ACA imposed a requirement on manufacturers of branded drugs and biologic agents to provide a 50% discount off the negotiated price of branded drugs dispensed to Medicare Part D beneficiaries in the coverage gap (i.e., "donut hole").
- The ACA imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications.
- The ACA included the Federal Physician Payments Sunshine Act, which requires certain pharmaceutical manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exception, to track certain financial arrangements with physicians and teaching hospitals, including any "transfer of value" provided, as well as any ownership or investment interests held by physicians and their immediate family members. Covered manufacturers were required to begin collecting data on August 1, 2013 and submit reports on aggregate payment data to CMS for the first reporting period (August 1, 2013—December 31, 2013) by March 31, 2014, and were required to report detailed payment data for the first reporting period and submit legal attestation to the completeness and accuracy of such data by June 30, 2014. Thereafter, covered manufacturers must submit reports by the 90th day of each subsequent calendar year. The information reported was made publicly available on a searchable website in September 2014.

- The ACA established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products.
- The ACA created the Independent Payment Advisory Board which has the authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. Under certain circumstances, these recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings.
- The ACA established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to improve quality of care and lower program costs of Medicare, Medicaid and the Children's Health Insurance Program, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation through 2019.

Many of the details regarding the implementation of the ACA are yet to be determined, and at this time, it remains unclear the full effect that the ACA would have on our business.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, 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 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability.

European Union Drug Development

In the European Union, our products will also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if an MAA from the competent regulatory agencies has been obtained, and the various phases of preclinical and clinical research in the European Union are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trial regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved by two distinct bodies in each of the EU countries where the trial is to be conducted: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. In addition, all serious adverse reactions to the investigated drug that occur during the clinical trial must be reported to the NCA and ECs of the Member State where they occurred.

The EU clinical trials legislation is currently undergoing a revision process mainly aimed at making more uniform and streamlining the clinical trials authorization process, simplifying adverse event reporting procedures, improving the supervision of clinical trials and increasing the transparency of clinical trials.

European Union Drug Review Approval

In the European Economic Area, or EEA, which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining an MAA. There are two types of MAAs: the Community MAA, which is issued by the European Commission through the Centralized Procedure based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, a body of the EMA, and which is valid throughout the entire territory of the EEA; and the National MAA, which is issued by the competent authorities of the Member States of the EEA and only authorized marketing in that Member State's national territory and not the EEA as a whole.

The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU. The National MAA is for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this

National MAA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MAA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MAA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. If the RMS proposes to authorize the product, and the other Member States do not raise objections, the product is granted a national MAA in all the Member States where the authorization was sought. Before granting the MAA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Other Regulations

We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control and disposal of hazardous or potentially hazardous substances. We may incur significant costs to comply with such laws and regulations now or in the future.

Employees

We had twenty-four employees as of March 1, 2017. None of our employees are represented by any collective bargaining unit. We believe that we maintain good relations with our employees.

Corporate Information

We were incorporated in Delaware in 1999. Our principal executive offices are located at 91 Hartwell Avenue, Lexington, MA 02421, and our telephone number is (781) 676-2100. Our internet address is www.inotekpharma.com. We use our website as means of disclosing material non-public information and for complying with our disclosure obligations under Regulation FD. We make available on our website, free of charge, our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Our SEC reports can be accessed through the Investors section of our website. Further, a copy of this Annual Report on Form 10-K is located at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D. C. 20549. Information on the operation of the Public Reference Room can be obtained by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains reports, proxy and information statements and other information regarding our filings at www.sec.gov. The information found on our website is not incorporated by reference into this report or any other report we file with or furnish to the SEC. Our common stock is listed on the NASDAQ Global Market under the symbol "ITEK."

Research and Development

For the years ended December 31, 2016, 2015 and 2014, our research and development expenses were $32.0 million, $12.6 million and $5.6 million, respectively.

Item 1A. Risk Factors

We operate in an industry that involves numerous risks and uncertainties. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes hereto. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects. The risks and uncertainties described below may change over time and other risks and uncertainties, including those that we do not currently consider material, may impair our business. In these circumstances, the market price of our common stock could decline.

Risks Related to Our Financial Position and Need for Additional Capital

We currently have no source of revenue and may never become profitable.

We are a clinical-stage biopharmaceutical company with a limited operating history. Our ability to generate revenue and become profitable depends upon our ability to successfully complete the development of our product candidates for the treatment of glaucoma and obtain the necessary regulatory approvals for our product candidates. We have never been profitable, have no products approved for commercial sale and to date have not generated any revenue from product sales. Even if we receive regulatory approval for the sale of our product candidates, we do not know when such product candidates will generate revenue, if at all. Our ability to generate product revenue depends on a number of factors, including our ability to:

- successfully complete clinical development, and receive regulatory approval, for our product candidates, including *trabodenoson* monotherapy and *trabodenoson* with *latanoprost* as a fixed-dose combination, or FDC;
- set an acceptable price for our product candidates and obtain coverage and adequate reimbursement from third-party payors;
- establish sales, marketing and distribution systems for our product candidates;
- add operational, financial and management information systems and personnel, including personnel to support our clinical, manufacturing and planned future commercialization efforts;
- have commercial quantities of our product candidates manufactured at acceptable cost levels;
- successfully market and sell our product candidates in the United States and enter into partnerships or other arrangements to commercialize our product candidates outside the United States; and
- maintain, expand and protect our intellectual property portfolio.

In addition, because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses, or when, or if, we will be able to achieve or maintain profitability. In addition, our expenses could increase beyond expectations if we are required by the U.S. Food and Drug Administration, or FDA, and comparable non-U.S. regulatory authorities, or other regulatory authorities to perform studies or clinical trials in addition to those that we currently anticipate. Even if our product candidates are approved for commercial sale, we anticipate incurring significant costs associated with the commercial launch of these products.

Our ability to become and remain profitable depends on our ability to generate revenue. Even if we are able to generate revenues from the sale of our product candidates, we may not become profitable and may need to obtain additional funding to continue operations. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations. 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 decrease the value of our Company and could impair our ability to raise capital, expand our business or continue our operations. A decline in the value of our Company could also cause you to lose all or part of your investment.

We have a history of net losses and anticipate that we will continue to incur net losses for the foreseeable future.

We have a history of losses and anticipate that we will continue to incur net losses for the foreseeable future. Our net losses were $42.9 million, $68.0 million and $9.5 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of $238.9 million.

Investment in pharmaceutical product development is highly speculative because it entails substantial upfront expenditures and significant risk that a product candidate will fail to gain regulatory approval or become commercially viable. We have devoted most of our financial resources to research and development, including our non-clinical development activities and clinical trials. We are not currently generating revenues, and we cannot estimate with precision the extent of our future losses. We do not currently have any products that are available for commercial sale and we may never generate revenue from selling products or achieve profitability. We

expect to continue to incur substantial and increasing losses through the projected commercialization of our product candidates. None of our product candidates have been approved for marketing in the United States and may never receive such approval. As a result of these factors, we are uncertain when or if we will achieve profitability and, if so, whether we will be able to sustain it. Our ability to produce revenue and achieve profitability is dependent on our ability to complete the development of our product candidates, obtain necessary regulatory approvals, and have our products manufactured and successfully marketed. We cannot assure you that we will be profitable even if we successfully commercialize our products. Failure to become and remain profitable may adversely affect the market price of our common stock and our ability to raise capital and continue operations.

In February 2015, we completed our initial public offering of 6,667,000 shares of our common stock at a price of $6.00 per share and a concurrent offering of $20.0 million aggregate principal amount of 5.0% Convertible Senior Notes due in 2020, or the 2020 Convertible Notes. In March 2015, the underwriters exercised 299,333 shares of common stock at $6.00 per share and $1.0 million of the 2020 Convertible Notes pursuant to their overallotment options. We received net proceeds of approximately $36.5 million, after deducting underwriting discounts and offering-related costs, from our equity issuances and approximately $18.9 million in net proceeds, after deducting underwriting discounts and offering-related costs, from our debt issuances.

In August 2015, we completed an underwritten public offering of our common stock, or the Follow-on Offering. We issued 6,210,000 shares of our common stock at a price of $12.75 per share, including 810,000 shares from the underwriters' full exercise of their overallotment option, and we received net proceeds of $74.0 million, after deducting underwriting discounts and offering-related costs.

In 2016, we sold 482,689 shares of common stock pursuant to our ATM and received net proceeds of $4.0 million.

In August 2016, we closed an underwritten public offering of $52.0 million aggregate principal amount of 5.75% Convertible Senior Notes due 2021, including $2.0 million from an exercise of the underwriters' overallotment option, or the 2021 Convertible Notes, and received net proceeds of approximately $48.7 million after deducting underwriting discounts and offering-related costs. (See Note 5 in the accompanying notes to the financial statements).

We expect our research and development expenses to continue to be significant in connection with our product development activities, including our Phase 2 clinical trial for our FDC product candidate which commenced in July 2016, and our planned Phase 3 programs. In addition, if we obtain regulatory approval for our product candidates, we expect to incur increased sales and marketing expenses. As a result, we expect to continue to incur significant and increasing operating losses and negative cash flows for the foreseeable future. These losses have had and will continue to have a material adverse effect on our stockholders' deficit, financial position, cash flows and working capital.

We will need to obtain additional financing to fund our operations and, if we are unable to obtain such financing, we may be unable to complete the development and commercialization of our primary product candidates.

Our operations have consumed substantial amounts of cash since inception. As of December 31, 2016, our cash and cash equivalents and short-term investments aggregated $126.5 million. We estimate that these funds will be sufficient to fund our projected operating requirements into 2019. We will need to obtain additional financing to conduct additional trials for the approval of our drug candidates and complete the development of any additional product candidates we might acquire. Moreover, our fixed expenses such as rent and other contractual commitments are substantial and may increase in the future.

Adequate additional funding may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future potential commercialization efforts. Our forecast of the period of time through which our financial resources will be adequate to support our operating requirements is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors, including the factors discussed elsewhere in this "Risk Factors" section. We have based this forecast on a number of assumptions that may prove to be wrong, and changing circumstances beyond our control may cause us to consume capital more rapidly than we currently anticipate.

Our future funding requirements will depend on many factors, including, but not limited to:

- the progress, timing, scope and costs of our clinical trials, including the ability to enroll patients in our planned and potential future clinical trials in a timely manner;
- the time and cost necessary to obtain regulatory approvals that may be required by regulatory authorities;
- our ability to successfully commercialize our product candidates;

- the amount of sales and other revenues from product candidates that we may commercialize, if any, including the selling prices for such product candidates and the availability of coverage and adequate reimbursement from third parties;
- selling and marketing costs associated with our product candidates, including the cost and timing of expanding our marketing and sales capabilities;
- the terms and timing of any potential future collaborations, licensing or other arrangements that we may establish;
- cash requirements of any future acquisitions and/or the development of other product candidates;
- the costs of operating as a public company;
- the time and cost necessary to respond to technological and market developments;
- the costs of maintaining and expanding our existing intellectual property rights; and
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

Until we can generate a sufficient amount of revenue, we may finance future cash needs through public or private equity offerings, license agreements, debt financings, collaborations, strategic alliances, marketing or distribution arrangements or a combination thereof. Additional funds may not be available when we need them on terms that are acceptable to us, or at all. General market conditions or the market price of our common stock may not support capital raising transactions such as an additional public or private offering of our common stock or other securities. In addition, our ability to raise additional capital may be dependent upon our stock being quoted on The NASDAQ Global Market, or NASDAQ, or upon obtaining shareholder approval. There can be no assurance that we will be able to satisfy the criteria for continued listing on NASDAQ or that we will be able to obtain shareholder approval if it is necessary. If adequate funds are not available, we may be required to delay or reduce the scope of or eliminate one or more of our research or development programs or our commercialization efforts.

We may seek to access the public or private capital markets whenever conditions are favorable, even if we do not have an immediate need for additional capital at that time. In addition, if we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or to grant licenses on terms that may not be favorable to us. Our inability to obtain additional funding when we need it could seriously harm our business.

Additional capital that we may need to operate or expand our business may not be available.

We may require additional capital to operate or expand our business. If we raise additional funds through the issuance of equity or convertible securities, the percentage ownership of holders of our common stock could be significantly diluted and these newly issued securities may have rights, preferences or privileges senior to those of holders of our common stock. Furthermore, volatility in the credit or equity markets may have an adverse effect on our ability to obtain debt or equity financing or the cost of such financing. If we do not have funds available to enhance our solution, maintain the competitiveness of our technology and pursue business opportunities, this could have an adverse effect on our business, operating results and financial condition.

The indenture governing our 2021 Convertible Notes contain restrictions that will limit our operating flexibility, and we may incur additional debt in the future that may include similar or additional restrictions.

The indenture governing our 2021 Convertible Notes contain covenants that, among other things, restrict our and our subsidiaries' ability to take specific actions, even if we believe them to be in our best interest. These covenants include restrictions on our ability and the ability of our future subsidiaries to incur additional indebtedness and issue certain types of preferred stock, other than certain permitted indebtedness and preferred stock. In addition, the indenture governing our 2021 Convertible Notes will include a covenant that limits our ability to merge or consolidate with other entities in certain circumstances. These covenants and restrictions limit our operational flexibility and could prevent us from taking advantage of business opportunities as they arise, growing our business or competing effectively.

A breach of any of these covenants or other provisions in our future debt agreements could result in an event of default, which if not cured or waived, could result in the 2021 Convertible Notes or such debt becoming immediately due and payable. This, in turn, could cause any of our other debt existing at such time to become due and payable as a result of cross-default or cross-acceleration provisions contained in the agreements governing such other debt. In the event that some or all of our debt is accelerated and becomes immediately due and payable, we may not have the funds to repay, or the ability to refinance, such debt.

Servicing our debt requires a significant amount of cash, and we may not have sufficient cash flow from our business to pay our substantial debt.

We currently have no source of revenue. Our ability to make scheduled payments of the principal of, to pay interest on or to refinance our indebtedness, including the 2021 Convertible Notes, depends on our future performance, which is subject to economic, financial, competitive and other factors, most of which are beyond our control. Our business has not historically generated cash flow from operating activities and may not in the future generate cash flow from operating activities sufficient to service our obligations under our 2021 Convertible Notes and any future indebtedness we may incur and to make necessary capital expenditures. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as reducing or delaying investments or capital expenditures, selling assets, restructuring debt or obtaining additional equity capital on terms that may be onerous or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations.

We may not have the ability to raise the funds necessary to repurchase our 2021 Convertible Notes upon a fundamental change, and our future debt may contain limitations on our ability to repurchase the 2021 Convertible Notes.

Holders of our 2021 Convertible Notes have the right to require us to repurchase their 2021 Convertible Notes upon the occurrence of a fundamental change, the occurrence of certain change of control transactions or delisting events, at a fundamental change repurchase price equal to 100% of the principal amount of the 2021 Convertible Notes to be repurchased, plus accrued and unpaid interest, if any, to, but not including, the fundamental change repurchase date. However, we may not have enough available cash or be able to obtain financing at the time we are required to make repurchases of 2021 Convertible Notes surrendered therefor. In addition, our ability to repurchase the 2021 Convertible Notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase 2021 Convertible Notes at a time when the repurchase is required by the indenture would constitute a default under the indenture. A default under the indenture or the fundamental change itself could also lead to a default under agreements governing our future indebtedness, if any. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and repurchase the 2021 Convertible Notes.

The fundamental change repurchase feature of our 2021 Convertible Notes may delay or prevent an otherwise beneficial attempt to take over our company.

The terms of our 2021 Convertible Notes require us to repurchase the 2021 Convertible Notes in cash in the event of a fundamental change. A takeover of our company, if such takeover constituted a “fundamental change,” would trigger an option of the holders of the 2021 Convertible Notes to require us to repurchase the 2021 Convertible Notes. This may have the effect of delaying or preventing a takeover of our company that would otherwise be beneficial to investors in the 2021 Convertible Notes.

Risks Related to Development, Potential Regulatory Approval and Commercialization

We depend substantially on the success of our product candidates, particularly trabodenoson monotherapy and trabodenoson FDC, which are still in development. We may be unable to successfully develop and commercialize our product candidates, especially in light of our MATrX-1 clinical trial’s failure to meet its primary endpoint, or may experience significant delays in doing so, which would materially harm our business.

Our business and the ability to generate revenue related to product sales, if ever, will depend on the successful development, formulation and manufacturing, regulatory approval and commercialization of our product candidates *trabodenoson* monotherapy and *trabodenoson* FDC, which are still in development, and other potential products we may develop or license. In January 2017, we announced top-line data from our MATrX-1 pivotal Phase 3 clinical trial, which failed to meet its primary endpoint. MATrX-1 did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute IOP from placebo at every single one of the 12 time points comprising the primary endpoint. This was due to a larger than expected treatment effect in the placebo/vehicle group, as compared to both our prior Phase 2 data and a recent meta-analysis examining placebo responses from 10 placebo-controlled trials, which showed a placebo/vehicle result of -2.01 mmHg (Raber, et al). During analysis of the IOP data from the trial, a treatment-by-site interaction was found where a small number of sites (4 sites out of a total of 55) caused an important change in the expected vehicle results. The review of the MATrX-1 data is ongoing and upon completion of all analyses, we plan to request a meeting with the FDA in the first half of 2017 to discuss these findings. While we believe these results, along with further exploratory analyses, will be integral in determining the path forward for our *trabodenoson* monotherapy, there can be no assurance that we will be able to pursue further development efforts or obtain regulatory approval.

We have invested a significant portion of our efforts and financial resources in the development of our existing product candidates. The success of our product candidates will depend on several factors, including:

- successful completion of clinical trials, and the supporting non-clinical toxicology, formulation development, and manufacturing of supplies for the clinical program in accordance with current Good Manufacturing Practices, or cGMP;
- receipt of regulatory approvals from the FDA and other applicable regulatory authorities outside the United States;
- maintenance of existing relationships and establishment of arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity;
- protecting our rights in our intellectual property;
- launching commercial sales of our product candidates, if and when approved;
- acceptance of any approved product by the medical community and patients;
- obtaining coverage and adequate reimbursement from third-party payors for product candidates, if and when approved;
- effectively competing with other products; and
- achieving a continued acceptable safety and efficacy profile for our product candidates following regulatory approval, if and when received.

If we 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 develop and commercialize our product candidates, which would materially harm our business and we may not be able to earn sufficient revenues and cash flows to continue our operations.

Our product candidates are *trabodenoson* as a monotherapy and as an FDC consisting of *trabodenoson* with a prostaglandin analog, or PGA. We have no other product candidates in our near term product pipeline. As a result, we are substantially dependent on the successful development and commercialization of *trabodenoson*. The results of our chronic toxicology program could identify a safety problem, or our current and upcoming pivotal trials of *trabodenoson* monotherapy or our current Phase 2 program for the FDC product candidate could fail to demonstrate efficacy in lowering IOP, especially in light of our Phase 3 results, or could identify safety issues related to *trabodenoson*, which would materially and adversely affect our development strategy.

Our MATrX-1 pivotal Phase 3 trial of trabodenoson for the treatment of primary open-angle glaucoma or ocular hypertension did not meet the primary endpoint, which could continue to harm our business and further disappoint our stockholders and cause the trading price of our common stock to continue to decrease.

Our lead product candidate in development is *trabodenoson* for the treatment of primary open-angle glaucoma or ocular hypertension. In January 2017, we announced top-line data from our MATrX-1 pivotal Phase 3 clinical trial, which failed to meet its primary endpoint. Currently, management in conjunction with its clinical and regulatory advisors are evaluating the clinical and regulatory pathway forward, although this is subject to ongoing review and evaluation. No assurance can be given that a clinical and regulatory pathway forward will be possible without significantly more capital invested in the Company or will otherwise be successful. Further, no assurance can be given that additional capital would be available or that such capital would be available at acceptable terms.

We have not obtained regulatory approval for any of our product candidates in the United States or in any other country.

We currently do not have any product candidates that have gained regulatory approval for sale in the United States or in any other country, and we cannot guarantee that we will ever have marketable products. Our business is substantially dependent on our ability to complete the development of, obtain regulatory approval for and successfully commercialize product candidates in a timely manner. We cannot commercialize product candidates in the United States without first obtaining regulatory approval to market each product from the FDA; similarly, we cannot commercialize product candidates outside of the United States without obtaining regulatory approval from comparable foreign regulatory authorities. We have completed a Phase 2 trial in which we tested *trabodenoson* co-administered with *latanoprost*. We attended an End-of-Phase 2 meeting with the FDA for *trabodenoson* monotherapy in the first half of 2015 and initiated a pivotal Phase 3 program in the fourth quarter of 2015, which consists of two Phase 3 monotherapy pivotal trials and a long-term safety study. We completed our initial Phase 3 trial and reported top-line data on January 3, 2017. Because the primary endpoint of the trial was not met, we plan to discuss with the FDA the subsequent necessary steps needed to attain marketing approval of *trabodenoson* monotherapy for the treatment of glaucoma in the United States. We cannot predict whether any of our future trials, including our planned long-term safety trial of *trabodenoson*, will be successful or whether regulators will agree with our conclusions regarding the preclinical studies and clinical trials we have conducted to date or

will conduct. Moreover, any determination of changes in a study design and its confirmation with the FDA could result in a significant range of costs for the Phase 3 pivotal and long-term safety trials.

Before obtaining regulatory approvals for the commercial sale of any product candidate for a target indication, we must demonstrate in preclinical studies and well-controlled clinical trials, and, with respect to approval in the United States, to the satisfaction of the FDA, that the product candidate is safe and effective for use for that target indication and that the manufacturing facilities, processes and controls are adequate. In the United States, we have not submitted a New Drug Application, or NDA, for any of our product candidates. An NDA must include extensive preclinical and clinical data and supporting information to establish the product candidate's safety and effectiveness for each desired indication. The NDA must also include significant information regarding the chemistry, manufacturing and controls for the product. Obtaining approval of an NDA is a lengthy, expensive and uncertain process, and approval may not be obtained. If we submit an NDA to the FDA, the FDA must decide whether to accept or reject the submission for filing. We cannot be certain that any submissions will be accepted for filing and reviewed by the FDA or, if accepted and reviewed, will be approved.

Regulatory authorities outside of the United States, such as in Europe and Japan and in emerging markets, also have requirements for approval of drugs for commercial sale with which we must comply prior to marketing in those areas. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our product candidates. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and obtaining regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking non-U.S. regulatory approval could require additional non-clinical studies or clinical trials, which could be costly and time consuming. The non-U.S. regulatory approval process may include all of the risks associated with obtaining FDA approval or additional risks. For all of these reasons, we may not obtain non-U.S. regulatory approvals on a timely basis, if at all.

The process to develop, obtain regulatory approval for and commercialize product candidates is long, complex and costly both inside and outside of the United States, and approval is never guaranteed. Even if our product candidates were to successfully obtain approval from the regulatory authorities, any approval might significantly limit the approved indications for use, or require that precautions, contraindications, or warnings be included on the product labeling, or require expensive and time-consuming post-approval clinical trials or surveillance as conditions of approval. Following any approval for commercial sale of our product candidates, certain changes to the product, such as changes in manufacturing processes and additional labeling claims, will be subject to additional FDA review and approval. Also, regulatory approval for any of our product candidates may be withdrawn. If we are unable to obtain regulatory approval for our product candidates in one or more jurisdictions, or any approval contains significant limitations, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed. Furthermore, we may not be able to obtain sufficient funding or generate sufficient revenue and cash flows to continue the development of any other product candidate in the future.

We are reevaluating our clinical and regulatory pathway forward for our trabodenoson monotherapy product candidate, and our product candidate might not be approved by regulatory authorities or introduced commercially for at least several years, if at all.

In January 2017, we announced disappointing top-line data from our MATrX-1 pivotal Phase 3 clinical trial, which failed to meet its primary endpoint. Currently, management in conjunction with its clinical and regulatory advisors are evaluating the clinical and regulatory pathway forward based on the data from the MATrX-1 trial. Going forward, *trabodenoson* will require further development and clinical testing and investment prior to obtaining required regulatory approvals, if ever, and commercialization in the United States and abroad. We cannot provide assurance that a new clinical and regulatory pathway will be successful or that *trabodenoson* will be developed successfully. Even if a viable clinical and regulatory pathway forward is identified, we cannot provide assurance that *trabodenoson* will:

- prove to be safe and effective in clinical studies;
- meet applicable regulatory standards or obtain required regulatory approvals;
- demonstrate substantial protective or therapeutic benefits in the prevention or treatment of any disease;
- be capable of being produced in commercial quantities at reasonable costs;
- obtain coverage and favorable reimbursement rates from insurers and other third-party payors; or
- be marketed successfully or achieve market acceptance by physicians and patients.

Regulatory approval may be substantially delayed or may not be obtained for one or all of our product candidates if regulatory authorities require additional time or studies to assess the safety and efficacy of our product candidates.

We may be unable to initiate or complete development of our product candidates on schedule, if at all. To complete the studies for our product candidates, we will require additional funding. In addition, if regulatory authorities require additional time or studies to assess the safety or efficacy of our product candidates, we may not have or be able to obtain adequate funding to complete the necessary steps for approval for any or all of our product candidates. Preclinical studies and clinical trials required to demonstrate the safety and efficacy of our product candidates are time consuming and expensive and together take several years or more to complete. Delays in regulatory approvals or rejections of applications for regulatory approval in the United States, Europe, Japan or other markets may result from many factors, including:

- our inability to obtain sufficient funds required for a clinical trial;
- requests from regulatory authorities for additional analyses, reports, data, non-clinical and preclinical studies and clinical trials;
- questions from regulatory authorities regarding interpretations of data and results and the emergence of new information regarding our product candidates or other products;
- clinical holds, other regulatory objections to commencing or continuing a clinical trial or the inability to obtain regulatory approval to commence a clinical trial in countries that require such approvals;
- failure to reach agreement with the FDA or comparable non-US regulatory authorities regarding the scope or design of our clinical trials;
- our inability to manufacture in a timely manner or obtain from third parties sufficient quantities or quality of the product candidates or other materials required for a clinical trial;
- our inability to enroll a sufficient number of patients who meet the inclusion and exclusion criteria in our clinical trials. For example, we are seeking patients with elevated levels of IOP for our clinical trials, which are more difficult to find;
- our inability to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- our inability to reach agreements on acceptable terms with prospective contract research organizations, or CROs, and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- our inability to identify and maintain a sufficient number of trial sites, many of which may already be engaged in other clinical trial programs, including some that may be for the same indications targeted by our product candidates;
- any determination that a clinical trial presents unacceptable health risks;
- lack of adequate funding to continue the clinical trial due to unforeseen costs or other business decisions;
- our inability to obtain approval from Institutional Review Boards, or IRBs, to conduct clinical trials at their respective sites;
- difficulty in maintaining contact with patients after treatment, resulting in incomplete data; and
- unfavorable or inconclusive results of clinical trials and supportive non-clinical studies, including unfavorable results regarding the effectiveness of product candidates during clinical trials.

Changes in regulatory requirements and guidance may also occur and we may need to amend clinical trial protocols submitted to applicable regulatory authorities to reflect these changes. Amendments may require us to resubmit clinical trial protocols to IRBs for re-examination, which may impact the costs, timing or successful completion of a clinical trial.

If the FDA requires us to change the design of our planned pivotal trials, the actual costs of these trials may be greater than what we estimated based on our current expectations regarding the design of these trials. If we are required to conduct additional clinical trials or other studies with respect to any of our product candidates beyond those that we initially contemplated, if we are unable to successfully complete our clinical trials or other studies or if the results of these studies are not positive or are only modestly positive, we may be delayed in obtaining regulatory approval for that product candidate, we may not be able to obtain regulatory approval at all or we may obtain approval for indications that are not as broad as intended. Our product development costs will also increase if we experience delays in testing or approvals and we may not have sufficient funding to complete the testing and approval process. Significant clinical trial delays could allow our competitors to bring products to market before we do and impair our ability to commercialize our products if and when approved. If any of this occurs, our business will be materially harmed.

We have successfully formulated our fixed-dose combination product candidate in a way that is suitable for Phase 2 clinical use. However, we have not successfully manufactured the product at commercial scale, nor completed stability testing to confirm its acceptability for commercial use. Any such delay or failure could materially harm our commercial prospects, result in higher costs and deprive us of product candidate revenues.

We completed a Phase 2 trial and are currently conducting an additional Phase 2 trial to evaluate the efficacy, tolerability and safety of *trabodenoson* when co-administered with commercially-available *latanoprost* eye drops. We have formulated our FDC product candidate to include these two drugs in a single eye drop. However, we may never be able to formulate or manufacture our FDC product candidate at commercial scale, or be able to demonstrate that the product is stable enough to commercialize. Any delay or failure to develop a suitable product formulation or manufacturing process for our FDC product candidate could materially harm our commercial prospects, result in higher costs or deprive us of potential product revenues.

Failure can occur at any stage of clinical development. If the clinical trials for our product candidates are unsuccessful, we could be required to abandon development.

A failure of one or more clinical trials can occur at any stage of testing for a variety of reasons. The outcome of preclinical testing and early clinical trials may not be predictive of the outcome of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. In addition, adverse events may occur or other risks may be discovered in any clinical trials that will cause us to suspend or terminate our clinical trials. In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including but not limited to changes in or adherence to trial protocols, differences in size and type of the patient populations and the rates of dropout among clinical trial participants. We have exposed 414 clinical trial subjects to *trabodenoson*. The FDA expects that a total of at least 1,300 patients will be exposed to at least a single dose of *trabodenoson* before submission of an NDA, and the complete NDA submission package must also contain safety data from at least 300 patients treated with *trabodenoson* for at least six months, and at least 100 patients treated for at least a year. Our future clinical trial results therefore may not demonstrate safety and efficacy sufficient to obtain regulatory approval for our product candidates. Moreover, we still need to evaluate the long-term safety effects of our product candidates, the results of which could adversely affect our clinical development program.

Flaws in the design of a clinical trial may not become apparent until the clinical trial is well-advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. In addition, clinical trials often reveal that it is not practical or feasible to continue development efforts. Further, we have never submitted an NDA for any product candidates.

We may voluntarily suspend or terminate our clinical trials if at any time we believe that they present an unacceptable risk to participants. Further, regulatory agencies and IRBs may at any time order or data safety monitoring boards may at any time recommend to the sponsor the temporary or permanent discontinuation of our clinical trials or request that we cease using investigators in the clinical trials if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements, or that they present an unacceptable safety risk to participants.

If the results of our clinical trials for our current product candidates or clinical trials for any future product candidates do not achieve the primary efficacy endpoints or demonstrate unexpected safety issues, the prospects for approval of our product candidates will be materially adversely affected. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have failed to achieve similar results in later clinical trials, including longer term trials, or have failed to obtain regulatory approval of their product candidates. Many compounds that initially showed promise in clinical trials or earlier stage testing have later been found to cause undesirable or unexpected adverse effects that have prevented further development of the compound. In addition, we have typically only tested our product candidates in a single eye, which may not accurately predict the efficacy or safety of our product candidates when dosed in both eyes. Our recently completed Phase 3 did not produce the results that we expected, and potential future Phase 3 pivotal trials and long-term safety studies of *trabodenoson* monotherapy may not produce the results that we expect or desire. Our current and planned clinical trials are also designed to test the use of *trabodenoson* in combination with *latanoprost* in a single dosage form. Accordingly, the efficacy of our primary product candidates may not be similar or correspond directly to their efficacy when used as a monotherapy. Our current product candidates remain subject to the risks associated with clinical drug development as indicated above.

In addition to the circumstances noted above, we may experience numerous unforeseen events that could cause our clinical trials to be delayed, suspended or terminated, or which could delay or prevent our ability to receive regulatory 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 implement a clinical hold;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators or IRBs may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- we may elect or be required to suspend or terminate clinical trials of our product candidates based on a finding that the participants are being exposed to health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- 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; and
- our product candidates may have undesirable adverse effects or other unexpected characteristics.

If we elect or are required to suspend or terminate a clinical trial of any of our product candidates, our commercial prospects will be adversely impacted and our ability to generate product revenues may be delayed or eliminated.

Our product candidates may have undesirable adverse effects, which may delay or prevent regulatory approval or, if approval is received, require our products to be taken off the market, require them to include safety warnings or otherwise limit their sales.

Unforeseen adverse effects from any of our product candidates could arise either during clinical development or, if approved, after the approved product has been marketed. In particular, we are aware of the known potential of adenosine and adenosine-like drugs to affect the heart if present in the systemic circulation at high enough levels.

Any undesirable adverse effects that may be caused by our product candidates could interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA and comparable non-U.S. regulatory authorities for any or all targeted indications, and in turn prevent us from commercializing our product candidates and generating revenues from their sale. In addition, if any of our product candidates receives regulatory approval and we or others later identify undesirable adverse effects caused by the product, we could face one or more of the following consequences:

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication, or other labeling changes;
- regulatory authorities may withdraw their approval of the product;
- regulatory authorities may seize the product;
- we may be required to change the way that the product is administered, conduct additional clinical trials or recall the product;
- regulatory authorities nay impose a REMS;
- we may be subject to litigation or product liability claims, fines, injunctions, or criminal penalties; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase the costs and expenses of commercializing such product, which in turn could delay or prevent us from generating significant revenues from its sale.

Trabodenoson is an adenosine mimetic. Adenosine is used therapeutically to manage cardiovascular arrhythmias, such as paroxysmal supraventricular tachycardia, a type of accelerated heart rate. All of our data to date reflects that *trabodenoson* does not have systemic effects, including no impact on the cardiovascular system when dosed in the eye. However, we are still conducting additional trials for *trabodenoson* and systemic effects may arise in future trials. Furthermore, if *trabodenoson* has the perception of having potential adverse effects because it is an adenosine mimetic, it may be negatively viewed by ophthalmologists and optometrists, patients, patient advocacy groups, third-party payors and the medical community which would adversely affect the market acceptance of our product candidates. In addition, the use of our product candidates outside the indications approved for use, or off-label use, or the use of our product candidate in an inappropriate manner, may increase the risk of injury to patients. If approved, clinicians may use our products for off-label uses, as the FDA does not restrict or regulate a clinician's choice of treatment within the practice of medicine. Off-label use of our products may increase the risk of product liability claims against us. Product liability claims are expensive to defend and could divert our management's attention and result in substantial damage awards against us.

If our product candidates receive regulatory approval, we will be subject to ongoing regulatory requirements and we may face future development, manufacturing and regulatory difficulties.

Our product candidates, if approved, will also be subject to ongoing regulatory requirements for labeling, packaging, storage, advertising, promotion, sampling, record-keeping, submission of safety and other post-market approval information, importation and exportation. In addition, approved products, manufacturers and manufacturers' facilities are required to comply with extensive FDA and European Medicines Agency, or EMA, requirements and the requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to cGMP requirements. As such, we and our potential future contract manufacturers will be subject to continual review and periodic inspections to assess compliance with cGMP. Accordingly, we and others with whom we work will be required to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control. We will also be required to report certain adverse reactions and production problems, if any, to the FDA, EMA and other similar foreign agencies and to comply with certain requirements concerning advertising and promotion for our product candidates. Promotional communications with respect to prescription drugs also are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Accordingly, once approved, we may not promote our products, if any, for indications or uses for which they are not approved.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, it may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters;
- require product recalls;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us or our potential future collaborators to enter into a consent decree or permanent injunction, which can include shutdown of manufacturing facilities, imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- impose other administrative or judicial civil or criminal penalties or pursue criminal prosecution;
- withdraw regulatory approval;
- refuse to approve pending applications or supplements to approved applications filed by us or by our potential future collaborators;
- impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products.

If we are unable to effectively establish a direct sales force in the United States, our business may be harmed.

We currently do not have an established sales organization and do not have a marketing or distribution infrastructure. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. If *trabodenoson* receives marketing approval in the United States, we plan to commercialize it by establishing a glaucoma-focused specialty sales force of approximately 150 people targeting high-prescribing ophthalmologists and optometrists throughout the United States. We will need to incur significant additional expenses and commit significant additional time and management resources to establish and train a sales force to market and sell our products. We may not be able to successfully establish these capabilities despite these additional expenditures.

Factors that may inhibit our efforts to successfully establish a sales force include:

- our inability to compete with other pharmaceutical companies to recruit, hire, train and retain adequate numbers of effective sales and marketing personnel with requisite knowledge of our target market;
- the inability of sales personnel to obtain access to adequate numbers of ophthalmologists and optometrists to prescribe any future approved products;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and
- a delay in bringing products to market after efforts to hire and train our sales force have already commenced.

In the event we are unable to successfully market and promote our products, our business may be harmed.

We currently intend to explore the licensing of commercialization rights or other forms of collaboration outside of the United States, which will expose us to additional risks of conducting business in international markets.

The non-U.S. markets are an important component of our growth strategy. If we fail to obtain licenses or enter into collaboration arrangements with selling parties, or if these parties are not successful, our revenue-generating growth potential will be adversely affected. Moreover, international business relationships subject us to additional risks that may materially adversely affect our ability to attain or sustain profitable operations, including:

- efforts to enter into collaboration or licensing arrangements with third parties in connection with our international sales, marketing and distribution efforts may increase our expenses or divert our management's attention from the acquisition or development of product candidates;
- changes in a specific country's or region's political and cultural climate or economic condition;
- differing regulatory requirements for drug approvals and marketing internationally, which could result in our being required to conduct additional clinical trials or other studies before being able to successfully commercialize our product candidates in any jurisdiction outside the United States;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;
- potentially reduced protection for intellectual property rights;
- potential third-party patent rights in countries outside of the United States;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability, particularly in non-U.S. economies and markets, including several countries in Europe;
- compliance with tax, employment, immigration and labor laws for employees traveling abroad;
- the effects of applicable foreign tax structures and potentially adverse tax consequences;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incidental to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally;
- failure of our employees and contracted third parties to comply with Office of Foreign Asset Control rules and regulations and the Foreign Corrupt Practices Act;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, volcanoes, typhoons, floods, hurricanes and fires.

These and other risks may materially adversely affect our ability to attain or sustain revenue from international markets.

We face competition from established branded and generic pharmaceutical companies and if our competitors are able to develop and market products that are preferred over our products, our commercial opportunity will be reduced or eliminated.

The development and commercialization of new drug products is highly competitive. We face competition from established branded and generic pharmaceutical companies, smaller biotechnology and pharmaceutical companies, as well as from academic institutions, government agencies and private and public research institutions, which may in the future develop products to treat glaucoma. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Glaukos Corporation recently commercialized a trabecular micro-bypass stent that is implanted in the eye during cataract surgery and allows fluid to flow from the anterior of the eye into the collecting channels, bypassing the TM. In addition, early-stage companies that are also developing glaucoma treatments may prove to be significant competitors, such as Aerie Pharmaceuticals, Inc., which is developing a Rho kinase/norepinephrine transport inhibitor. We expect that our competitors will continue to develop new glaucoma treatments, which may include eye drops, oral treatments, surgical procedures, implantable devices or laser treatments. Other early-stage companies may also compete through collaborative arrangements with large and established companies. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer adverse effects, are more convenient or are less expensive than our product candidates. The market for glaucoma prescriptions is highly competitive and is currently dominated by generic drugs, such as *latanoprost* and *timolol*, and additional products are expected to become available on a generic basis over the coming years. If any of our product candidates are approved, we expect that they will be priced at a premium over competitive generic products and consistent with other branded glaucoma drugs.

If our competitors market products that are more effective, safer, have fewer side effects or are less expensive than our product candidates or that reach the market sooner than our potential future products, if any, we may not achieve commercial success.

The commercial success of our product candidates will depend on the degree of market acceptance among ophthalmologists and optometrists, patients, patient advocacy groups, third-party payors and the medical community.

Our product candidates may not gain market acceptance among ophthalmologists and optometrists, patients, patient advocacy groups, third-party payors and the medical community. There are a number of available therapies marketed for the treatment of glaucoma. Some of these drugs are branded and subject to patent protection, but most others, including *latanoprost* and many beta blockers, are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by ophthalmologists and optometrists, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. Additionally, in patients with normal tension glaucoma whose IOP falls into the normal range, IOP is generally much more difficult to reduce. In these patients, *trabodenoson* may offer little or no clinical benefit, which may ultimately limit its utility in this subpopulation of glaucoma patients. The degree of market acceptance of our product candidates will depend on a number of factors, including:

- the market price, affordability and patient out-of-pocket costs of our product candidates relative to other available products, which are predominantly generics;
- the degree to which our product candidates obtain coverage and adequate reimbursement;
- the effectiveness of our product candidates as compared with currently available products and any products that may be approved in the future;
- patient willingness to adopt our product candidates in place of current therapies;
- varying patient characteristics including demographic factors such as age, health, race and economic status;
- changes in the standard of care for the targeted indications for any of our product candidates;
- the prevalence and severity of any adverse effects or perception of any potential side effects;
- limitations or warnings contained in a product candidate’s FDA-approved labeling;
- limitations in the approved clinical indications for our product candidates;
- relative convenience and ease of administration;
- the strength of our selling, marketing and distribution capabilities;
- the quality of our relationship with patient advocacy groups;

- sufficient third-party coverage and reimbursement; and
- product liability claims.

In addition, the potential market opportunity for our product candidates is difficult to precisely estimate. Our estimates of the potential market opportunity for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research reports and other surveys. If any of these assumptions proves to be inaccurate, then the actual market for our product candidates could be smaller than our estimates of our potential market opportunity. If the actual market for 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 fail to achieve market acceptance of our product candidates in the United States and abroad, our revenue will be more limited and it will be more difficult to achieve profitability.

If we fail to obtain and sustain coverage and an adequate level of reimbursement for our product candidates by third-party payors, potential future sales would be materially adversely affected.

The course of treatment for glaucoma patients primarily includes older drugs, and the leading products for the treatment of glaucoma currently in the market, including *latanoprost* and *timolol*, are available as generic brands. There will be no commercially viable market for our product candidates without coverage and adequate reimbursement from third-party payors, and any coverage and reimbursement policy may be affected by future healthcare reform measures. We cannot be certain that coverage and adequate reimbursement will be available for our product candidates or any other future product candidates we develop. Additionally, even if there is a commercially viable market, if the level of reimbursement is below our expectations, our anticipated revenue and gross margins will be adversely affected.

Third-party payors, such as government or private healthcare insurers, carefully review and increasingly question and challenge the coverage of and the prices charged for drugs. Reimbursement rates from private health insurance companies vary depending on the company, the insurance plan and other factors. Reimbursement rates may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. A current trend in the U.S. healthcare industry is toward cost containment. Large public and private payors, managed care organizations, group purchasing organizations and other similar organizations are exerting increasing influence on decisions regarding the use of, and reimbursement levels for, particular treatments. Such third-party payors, including Medicare, may question the coverage of, and challenge the prices charged for, medical products and services, and many third-party payors limit coverage of or reimbursement for newly approved healthcare products. In particular, third-party payors may limit the covered indications. Cost-control initiatives could decrease the price we might establish for our product candidates, which could result in product revenues being lower than anticipated. We believe our drugs will be priced significantly higher than existing generic drugs and consistently with current branded drugs. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. If we are unable to show a significant benefit relative to existing generic drugs, Medicare, Medicaid and private payors may not be willing to cover or provide adequate reimbursement for our drugs, which would significantly reduce the likelihood of them gaining market acceptance. In the United States, no uniform policy requirement for coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor.

We expect that private insurers will consider the efficacy, cost effectiveness, safety and tolerability of our product candidates in determining whether to approve coverage and set reimbursement levels for such products. Obtaining these approvals can be a time consuming and expensive process. Our business and prospects would be materially adversely affected if we do not receive approval for coverage and reimbursement of our product candidates from private insurers on a timely or satisfactory basis. Limitations on coverage and reimbursement could also be imposed by government payors, such as the local Medicare carriers, fiscal intermediaries, or Medicare Administrative Contractors. Further, Medicare Part D, which provides a pharmacy benefit to certain Medicare patients, does not require participating prescription drug plans to cover all drugs within a class of products. Our business could be materially adversely affected if private or governmental payors, including Medicare Part D prescription drug plans were to limit access to, or deny or limit reimbursement of, our product candidates or other potential products.

Reimbursement systems in international markets vary significantly by country and by region, and reimbursement approvals must be obtained on a country-by-country basis. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. For example, reimbursement in the European Union must be negotiated on a country-by-country basis and in many countries the product cannot be commercially launched until reimbursement is approved. The negotiation process in some countries can exceed 12 months. 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 products to other available therapies.

If the prices for our product candidates decrease or if governmental and other third-party payors do not provide coverage and adequate reimbursement levels, our revenue, potential for future cash flows and prospects for profitability will suffer.

Recently enacted and future legislation may increase the difficulty and cost of commercializing our product candidates and may affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay regulatory approval of our product candidates, restrict or regulate post-marketing activities and affect our ability to profitably sell our product candidates for which we obtain regulatory approval.

In March 2010, President Obama signed into law the ACA, a sweeping law intended to, among other things, broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Among other changes that affect the pharmaceutical industry, the ACA increased manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate amount for both branded and generic drugs and revised the definition of average manufacturer price, or AMP, which may also increase the amount of Medicaid drug rebates manufacturers are required to pay to states. The legislation also expanded Medicaid drug rebates, which previously had been payable only on fee-for-service utilization, to Medicaid managed care utilization, and created an alternative rebate formula for certain new formulations of certain existing products that is intended to increase the rebates due on those drugs. Further, the ACA imposed a significant annual fee on companies that manufacture or import branded prescription drug products and requires manufacturers to provide a 50% point-of-sale discount off the negotiated price of applicable branded drugs dispensed to beneficiaries in the Medicare Part D coverage gap, referred to as the "donut hole." Substantial new provisions affecting compliance have also been enacted, including the Physician Payments Sunshine Act, as described above. Although it is too early to determine the full effect of the ACA, the new law appears likely to continue the downward pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, 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 2012 through 2021, was unable to reach the required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability.

Legislative and regulatory proposals have been introduced at both the state and federal level to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We are not sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing approval testing and other requirements.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict whether future healthcare initiatives will be implemented at the federal or state level or in countries outside of the United States in which we may do business in the future, or the effect any future legislation or regulation will have on us.

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

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

If we are found in violation of federal or state "fraud and abuse" laws or other healthcare laws, we may face penalties, which may adversely affect our business, financial condition and results of operation.

In the United States, we are subject to various federal and state healthcare "fraud and abuse" laws, including anti-kickback laws, false claims laws and other laws intended, among other things, to reduce fraud and abuse in federal and state healthcare programs. The Federal Anti-Kickback Statute makes it illegal for any person or entity, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer or pay any remuneration, directly or indirectly, in cash or in kind, that is intended to induce or reward the referral of business, including the purchase, lease, order or arranging for or recommending the purchase, lease or order of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as Medicare or Medicaid. Although we seek to structure our business arrangements in compliance with all applicable requirements, many healthcare fraud and abuse laws are broadly written, and it may be difficult to determine precisely how the law will be applied in specific circumstances. Accordingly, it is possible that our practices may be challenged under the Federal Anti-Kickback Statute. The federal false claims and civil monetary penalties laws, including the civil False Claims Act prohibits any individual or entity from, among other things, knowingly presenting or causing to be presented for payment to the government, including the federal healthcare programs, claims for reimbursed drugs or services 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 civil False Claims Act has been interpreted to prohibit presenting claims for items or services that were not provided as claimed, or claims for medically unnecessary items or services. Cases have been brought under false claims laws alleging that off-label promotion of pharmaceutical products or the provision of kickbacks have resulted in the submission of false claims to governmental healthcare programs. In addition, private individuals have the ability to bring actions on behalf of the government under the civil False Claims Act as well as under the false claims laws of several states. Under the Health Insurance Portability and Accountability Act of 1996, or HIPAA, we are prohibited from, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private payors, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services to obtain money or property of any healthcare benefit program.

Additionally, the federal Physician Payments Sunshine Act within the Patient Protection and Affordable Care Act, as amended by the Health Care Education and Reconciliation Act, or collectively the ACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to certain payments or other transfers of value provided to physicians and teaching hospitals, and certain ownership and investment interests held by physicians and their immediate family members.

Many states have adopted laws similar to the aforementioned laws, including state anti-kickback and false claims laws, some of which apply to the referral of patients for healthcare services reimbursed by any source, not just governmental payors. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 U.S. Department of Health and Human Services Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There may be ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, including the Final Omnibus Rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information on certain types of individuals and organizations. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates, defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, many state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other and from HIPAA in significant ways and may not have the same effect, thus complicating compliance efforts.

Law enforcement authorities are increasingly focused on enforcing these laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that the government could allege violations of, or convict us of violating, these laws. If we are found in violation of one of these laws, we could be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion from governmental funded federal or state healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or

restructuring of our operations. Were this to occur, our business, financial condition and results of operations and cash flows may be materially adversely affected.

If we face allegations of noncompliance with the law and encounter sanctions, our reputation, revenues and liquidity may suffer, and our products could be subject to restrictions or withdrawal from the market.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenues from our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected. Additionally, if we are unable to generate revenues from our product sales, our potential for achieving profitability will be diminished and the capital necessary to fund our operations will be increased.

We may not be able to identify additional therapeutic opportunities for our product candidates or to expand our portfolio of products.

We may explore other therapeutic opportunities with *trabodenoson* and seek to develop and commercialize a portfolio of new ophthalmic drugs or explore non-ophthalmic opportunities in addition to our product candidates that we are currently developing. We have no potential products in our research and development pipeline other than those potential products that are formulations of *trabodenoson* or that apply *trabodenoson* for the treatment of glaucoma, other neuropathies and degenerative retinal diseases.

Research programs to pursue the development of our product candidates for additional indications and to identify new potential products or product candidates and disease targets require substantial technical, financial and human resources whether or not we ultimately are successful. Our research programs may initially show promise in identifying potential indications and/or potential products, yet fail to yield results for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential indications and/or potential products;
- product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs; or
- it may take greater human and financial resources to identify additional therapeutic opportunities for our product candidates or to develop suitable potential products through internal research programs and clinical trials than we will possess, thereby limiting our ability to diversify and expand our product portfolio.

Because we have limited financial and managerial resources, we focus on research programs and product candidates for specific indications. As a result, we may forego or delay pursuit of opportunities with other potential products or product candidates or for other indications that later prove to have greater commercial potential or a greater likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our product candidates or to develop suitable potential products through internal research programs, which could materially adversely affect our future growth and prospects.

If we reallocate our resources to acquire or develop one or more new product candidates, we may not be successful in developing such new product candidates and we will once again be subject to all the risks and uncertainties associated with research and development of products and technologies.

We have explored the possibility of reallocating our resources toward developing, acquiring, by acquisition or in-license, new product candidates. If we decide to acquire one or more new product candidates, we cannot guarantee that any such acquisition would result in the identification and successful development of one or more approved and commercially viable products. The development of products and technologies is subject to a number of risks and uncertainties, including:

- the time, costs and uncertainty associated with the clinical testing required to demonstrate the safety and effectiveness of a product candidate to obtain regulatory approvals;
- the ability to raise sufficient funds to fund the research and development of any one or more new product candidates;

- the ability to find third party strategic partners to assist or share in the costs of product development, and potential dependence on such strategic partners, to the extent Inotek may rely on strategic partners for future sales, marketing or distribution;
- the ability to protect the intellectual property rights associated with any one or more new product candidates;
- litigation;
- competition;
- ability to comply with ongoing regulatory requirements;
- government restrictions on the pricing and profitability of products in the United States and elsewhere; and
- the extent to which third-party payers, including government agencies, private health care insurers and other health care payers, such as health maintenance organizations, and self-insured employee plans, will cover and pay for newly approved therapies.

Risks Related to Our Reliance on Third Parties

We currently depend on third parties to conduct some of the operations of our clinical trials and other portions of our operations, and we may not be able to control their work as effectively as if we performed these functions ourselves.

We rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to oversee and conduct our clinical trials, and to perform data collection and analysis of our product candidates. We expect to rely on these third parties to conduct clinical trials of any other potential products that we develop. These parties are not our employees and we cannot control the amount or timing of resources that they devote to our program. In addition, any CRO that we retain will be subject to the FDA's regulatory requirements or similar foreign standards and we do not have control over compliance with these regulations by these providers. Our agreements with third-party service providers are on trial-by-trial and project-by-project bases. Typically, we may terminate the agreements with notice and occasionally the third party service provider may terminate the agreement without notice. Typically, we are responsible for the third party's incurred costs and occasionally we have to pay cancellation fees. If any of our relationships with our third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or regulatory approval of our product candidates or commercialization of our product candidates, producing additional losses and depriving us of potential product revenue.

Our reliance on these third parties for clinical development activities reduces our control over these activities but does not relieve us of our responsibilities, and we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan, the protocols for the trial and the FDA's regulations and international standards, referred to as Good Clinical Practice, or GCP, requirements, 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. Preclinical studies must also be conducted in compliance with other requirements, such as Good Laboratory Practice, or GLP, and the Animal Welfare Act. Managing performance of third-party service providers can be difficult, time consuming and cause delays in our development programs. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers.

Furthermore, these third parties may conduct clinical trials for competing drugs or may have relationships with other entities, some of which may be our competitors. As such, the ability of these third parties to provide services to us may be limited by their work with these other entities. The use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated.

If these third parties do not successfully carry out their contractual duties or obligations and meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols according to regulatory requirements or for other reasons, our financial results and the commercial prospects for our current product candidates or our other potential products could be harmed, our costs could increase and our ability to obtain regulatory approval and commence product sales could be delayed.

We have no manufacturing capacity or experience and anticipate continued reliance on third-party manufacturers for the development and commercialization of our product candidates in accordance with manufacturing regulations.

We do not currently, nor currently intend to, operate manufacturing facilities for clinical or commercial production of our product candidates. We have no experience in drug formulation, and we lack the resources and the capabilities to manufacture our product candidates and potential products on a clinical or commercial scale. We do not intend to develop facilities for the manufacture of product candidates for clinical trials or commercial purposes in the foreseeable future. We currently rely on third-party manufacturers to produce the active pharmaceutical ingredient and final drug product for our clinical trials. We currently have only one supplier of active pharmaceutical ingredient. We manage such production with all our vendors on a purchase order basis in accordance with applicable master service and supply agreements. We do not have long-term agreements with any of these or any other third-party suppliers. To the extent we terminate our existing supplier arrangements in the future and seek to enter into arrangements with alternative suppliers, we might experience a delay in our ability to obtain adequate supply for our clinical trials and commercialization. We also do not have any current contractual relationships for the manufacture of commercial supplies of any of our product candidates if and when they are approved. Our third-party manufacturers have made only a limited number of lots of our product candidates to date and have not made any commercial lots. The manufacturing processes for our product candidates have never been tested at commercial scale, and the process validation requirement has not yet been satisfied for any product candidate. These manufacturing processes and the facilities of our third-party manufacturers will be subject to inspection and approval by the FDA before we can commence the manufacture and sale of our product candidates, and thereafter on an ongoing basis. Some of our third-party manufacturers have never been inspected by the FDA and have not been through the FDA approval process for a commercial product. Some of our third-party manufacturers are subject to FDA inspection from time to time. Failure by these third-party manufacturers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidates may result in regulatory actions such as the issuance of FDA Form 483 inspectional observations, warning letters or injunctions or the loss of operating licenses. Based on the severity of the regulatory action, our clinical or commercial supply of our product candidates could be interrupted or limited, which could have a material adverse effect on our business.

With respect to commercial production of our product candidates in the future, we plan on outsourcing production of the active pharmaceutical ingredients and final product manufacturing if and when approved for marketing by the applicable regulatory authorities. This process is difficult and time consuming and we can give no assurance that we will enter commercial supply agreements with any contract manufacturers on favorable terms or at all.

Reliance on third-party manufacturers entails risks, including:

- manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of their agreements with us;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- the possible breach of the manufacturing agreement by the third party;
- product loss due to contamination, equipment failure or improper installation or operation of equipment or operator error;
- the failure of the third-party manufacturer to comply with applicable regulatory requirements; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

Our manufacturers may not perform as agreed or may not remain in the contract manufacturing business. In the event of a natural disaster, business failure, strike or other difficulty, we may be unable to replace a third-party manufacturer in a timely manner and the production of our product candidates and potential products could be interrupted, resulting in delays and additional costs. We may also have to incur other charges and expenses for products that fail to meet specifications and undertake remediation efforts.

If third-party manufacturers fail to comply with manufacturing regulations, our financial results and financial condition will be adversely affected.

Before a third party can begin the commercial manufacturing of our product candidates and potential products, their manufacturing facilities, processes and quality systems must be in compliance with applicable regulations. Due to the complexity of the processes used to manufacture pharmaceutical products and product candidates, any potential third-party manufacturer may be unable to initially pass federal, state or international regulatory inspections in a cost effective manner. If contract manufacturers fail to pass such inspection, our commercial supply of drug substance will be significantly delayed and may result in significant additional costs. In addition, pharmaceutical manufacturing facilities are continuously subject to inspection by the FDA and comparable non-U.S. regulatory authorities, before and after product approval, and must comply with cGMP. Our contract manufacturers may encounter difficulties in achieving quality control and quality assurance and may experience shortages in qualified personnel. In addition, contract manufacturers' failure to achieve and maintain high manufacturing standards in accordance with applicable regulatory requirements, or the incidence of manufacturing errors, could result in patient injury, product liability claims, product

shortages, product recalls or withdrawals, delays or failures in product testing or delivery, cost overruns or other problems that could seriously harm our business. If a third-party manufacturer with whom we contract is unable to comply with manufacturing regulations, we may also be subject to fines, unanticipated compliance expenses, recall or seizure of our products, product liability claims, total or partial suspension of production and/or enforcement actions, including injunctions, and criminal or civil prosecution. These possible sanctions could materially adversely affect our financial results and financial condition.

Furthermore, changes in the manufacturing process or procedure, including a change in the location where the product is manufactured or a change of a third-party manufacturer, will require prior FDA review and/or approval of the manufacturing process and procedures in accordance with the FDA's regulations, or comparable foreign requirements. This review may be costly and time consuming and could delay or prevent us from conducting our clinical trials or launching a product. The new facility will also be subject to pre-approval inspection. In addition, we have to demonstrate that the product made at the new facility is equivalent to the product made at the former facility by physical and chemical methods, which are costly and time consuming. It is also possible that the FDA may require clinical testing as a way to prove equivalency, which would result in additional costs and delay.

Any collaboration arrangement that we may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our current and future product candidates.

We plan to seek collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of our current and future product candidates outside of the United States. We will face, to the extent that we decide to enter into collaboration agreements, significant competition in seeking appropriate collaborators. Moreover, collaboration arrangements are complex and time consuming to negotiate, document and implement. We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements should we choose to enter into such arrangements, and the terms of the arrangements may not be favorable to us. If and when we collaborate with a third party for development and commercialization of a product candidate, we can expect to relinquish some or all of the control over the future success of that product candidate to the third party. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. To the extent such collaborators have programs that are competitive with our product candidates, they may decide to focus time and resources on development of those programs rather than our product candidates.

Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision making authority. Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

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

The development and potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

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

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or

commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Risks Related to Intellectual Property

We may not be able to protect our proprietary technology in the marketplace.

We depend on our ability to protect our proprietary technology. We rely largely on trade secret and patent laws, and confidentiality, licensing and other agreements with employees and third parties, all of which offer only limited protection. Our success depends in large part on our ability and any future licensee's ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We believe we will continue to be able to obtain, through prosecution of our current pending patent applications, adequate patent protection for our proprietary drug technology. If we are compelled to spend significant time and money protecting or enforcing our patents or patent applications, designing around patents held by others or licensing or acquiring, potentially for large fees, patents or other proprietary rights held by others, our business and financial prospects may be harmed. If we are unable to effectively protect the intellectual property that we own, other companies may be able to offer the same or similar products for sale, which could materially adversely affect our competitive business position and harm our business prospects. Our patents may be challenged, narrowed, invalidated, or circumvented, which could limit our ability to stop competitors from marketing the same or similar products or limit the length of term of patent protection that we may have for our products.

The patent positions of pharmaceutical products are often complex and uncertain. The breadth of claims allowed in pharmaceutical patents in the United States and many jurisdictions outside of the United States is not consistent. For example, in many jurisdictions the support standards for pharmaceutical patents are becoming increasingly strict. Some countries prohibit method of treatment claims in patents. Changes in either the patent laws or interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or create uncertainty. In addition, publication of information related to our current product candidates and potential products may prevent us from obtaining or enforcing patents relating to these product candidates and potential products, including, without limitation, composition-of-matter patents, which are generally believed to offer the strongest patent protection.

Our intellectual property consists of issued patents and pending patent applications related to our product candidates and other proprietary technology which cover compositions of matter, methods of use, combinations with other glaucoma products, formulations, polymorphs and the protection of the optic nerve. For *trabodenoson*, the composition patents are scheduled to expire in 2025 and 2026, in Europe and the United States, respectively. The *trabodenoson* polymorph US patent is scheduled to expire in 2033. See "Business—Intellectual Property" included in this Annual Report on Form 10-K for the year ended December 31, 2016, for further information about our issued patents and patent applications.

Patents that we own or may license in the future do not necessarily ensure the protection of our product candidates for a number of reasons, including without limitation the following:

- we may not have been the first to make the inventions covered by our patents or pending patent applications;
- we may not have been the first to file patent applications for these inventions;
- any patents issued to us may not cover our products as ultimately developed;
- our pending patent applications may not result in issued patents, and even if they issue as patents, they may not provide us with any competitive advantages, or may be challenged and invalidated by third parties;
- our patents may not be broad or strong enough to prevent competition from other products that are identical or similar to our product candidates;
- there can be no assurance that the term of a patent can be extended under the provisions of patent term extension afforded by U.S. law or similar provisions in foreign countries, where available;
- our patents, and patents that we may obtain in the future, may not prevent generic entry into the U.S. market for our *trabodenoson* and other product candidates;
- we may be required to disclaim part of the term of one or more patents;
- there may be prior art of which we are not aware that may affect the validity or enforceability of a patent claim;
- there may be patents issued to third parties that will affect our freedom to operate;

- if our patents are challenged, a court could determine that they are invalid or unenforceable;
- there might be significant changes in the laws that govern patentability, validity and infringement of our patents that adversely affects the scope of our patent rights;
- a court could determine that a competitor's technology or product does not infringe our patents;
- our patents could irretrievably lapse due to failure to pay fees or otherwise comply with regulations or could be subject to compulsory licensing; and
- we may fail to obtain patents covering important products and technologies in a timely fashion or at all.

In addition, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The United States Patent Office is currently developing 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 have not yet become effective. 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, in particular the first-to-file provision, 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, all of which could have a material adverse effect on our business and financial condition.

If we encounter delays in our development or clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced.

Our competitors may seek to invalidate our patents.

Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may seek to market generic versions of any approved products by submitting Abbreviated New Drug Applications, or ANDAs, to the FDA in which our competitors claim that our patents are invalid, unenforceable and/or not infringed. Alternatively, our competitors may seek approval to market their own products similar to or otherwise competitive with our products. In these circumstances, we may need to defend and/or assert our patents, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid and/or unenforceable. We may also fail to identify patentable aspects of our research and development before it is too late to obtain patent protection. Even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

The issuance of a patent is not conclusive as to its inventorship, scope, ownership, priority, validity or enforceability. In that regard, third parties may challenge our patents in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

A significant portion of our intellectual property portfolio currently includes pending patent applications that have not yet issued as patents. If our pending patent applications fail to issue our business will be adversely affected.

Our commercial success will depend significantly on maintaining and expanding patent protection for our product candidates, as well as successfully defending our current and future patents against third-party challenges. As of December 31, 2016, we own at least 50 issued patents and have at least 40 pending patent applications in the United States and a number of foreign jurisdictions relating to our current product candidates and proprietary technology. See "Business—Intellectual Property" included in this Annual Report on Form 10-K for the fiscal year ended December 31, 2016 for further information about our issued patents and patent applications. Our intellectual property consists of patents and pending patent applications related to our product candidates and other proprietary technology which cover compositions of matter, methods of use, combinations with other glaucoma products, formulations, polymorphs and the protection of the optic nerve. For *trabodenoson*, the composition of matter patents are scheduled to expire in 2025 and 2026, in Europe and the United States, respectively. The *trabodenoson* polymorph US patent is scheduled to expire in 2033.

There can be no assurance that our patent applications will issue as patents in the United States or foreign jurisdictions in which such applications are pending. Even if patents do issue on any of these applications, there can be no assurance that a third party will not challenge their validity or that we will obtain sufficient claim scope in those patents to prevent a third party from competing successfully with our products.

We may not be able to enforce our intellectual property rights throughout the world.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. To the extent we are able to obtain patents or other intellectual property rights in any foreign jurisdictions, it may be difficult for us to prevent infringement of our patents or misappropriation of these intellectual property rights. For example, some foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. In addition, changes in the law and legal decisions by courts in the United States and foreign countries may affect our ability to obtain adequate protection for our technology and the enforcement of intellectual property.

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

The United States Patent and Trademark Office, or the USPTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In this event, competitors might be able to enter the market earlier than would otherwise have been the case.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing our products.

Our commercial success depends significantly on our ability to operate without infringing the patents and other intellectual property rights of third parties. For example, there could be issued patents of which we are not aware that our product candidates or potential products infringe. There also could be patents that we believe we do not infringe, but that we may ultimately be found to infringe.

Moreover, patent applications are in some cases maintained in secrecy until patents are accepted or issued. The publication of discoveries in the scientific or patent literature frequently occurs substantially later than the date on which the underlying discoveries were made and patent applications were filed. Because patents can take many years to issue, there may be currently pending applications of which we are unaware that may later result in issued patents that our product candidates or potential products infringe. For example, pending applications may exist that claim or can be amended to claim subject matter that our product candidates or potential products infringe. Competitors may file continuing patent applications claiming priority to already issued patents in the form of continuation, divisional, or continuation-in-part applications, in order to maintain the pendency of a patent family and attempt to cover our product candidates.

Third parties may assert that we are employing their proprietary technology without authorization and may sue us for patent or other intellectual property infringement. These lawsuits are costly and could adversely affect our results of operations and divert the attention of managerial and scientific personnel. If we are sued for patent infringement, we would need to demonstrate that our product candidates, potential products or methods either do not infringe the claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity or unenforceability is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on us. In addition, we may not have sufficient resources to bring these actions to a successful conclusion. If a court holds that any third-party patents are valid, enforceable and cover our products or their use, the holders of any of these patents may be able to block our ability to commercialize our products unless we acquire or obtain a license under the applicable patents or until the patents expire. We may not be able to enter into licensing arrangements or make other arrangements at a reasonable cost or on reasonable terms. Any inability to secure licenses or alternative technology could result in delays in the introduction of our products or lead to prohibition of the manufacture or sale of products by us. Even if we are able to obtain a license, it may 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. In addition, in any such proceeding or litigation, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could

prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Any claims by third parties that we have misappropriated their confidential information or trade secrets could have a similar negative impact on our business. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations.

We may face claims of infringement, misappropriation or other violations of the rights of third-party intellectual property holders.

Pharmaceutical companies, biotechnology companies and academic institutions may compete with us in the commercialization of *trabodenoson* for use in ophthalmic indications and filing patent applications potentially relevant to our business. In order to contend with the strong possibility of third-party intellectual property conflicts, we periodically conduct freedom-to-operate studies, but such studies may not uncover all patents relevant to our business.

From time to time, we find it necessary or prudent to obtain licenses from third-party intellectual property holders. Where licenses are readily available at reasonable cost, such licenses are considered a normal cost of doing business. In other instances, however, we may use the results of freedom-to-operate studies to guide our early-stage research away from areas where we are likely to encounter obstacles in the form of third-party intellectual property. For example, where a third party holds relevant intellectual property and is a direct competitor, a license might not be available on commercially reasonable terms or available at all. We strive to identify potential third-party intellectual property issues in the early stages of research of our research programs, in order to minimize the cost and disruption of resolving such issues.

In spite of these efforts to avoid obstacles and disruptions arising from third-party intellectual property, it is impossible to establish with certainty that our products will be free of claims that we infringe, misappropriate or otherwise violate the rights of third-party intellectual property holders. Even with modern databases and online search engines, freedom-to-operate searches are imperfect and may fail to identify relevant patents and published applications. Even when a third-party patent is identified, we may conclude that we do not infringe the patent or that the patent is invalid. If the third-party patent owner disagrees with our conclusion and we continue with the business activity in question, patent litigation may result. We might decide to initiate litigation in an attempt to have a court declare the third-party patent invalid or non-infringed by our activity.

We may be subject to claims that we or our employees have misappropriated the intellectual property, including trade secrets, of a third party, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities, biotechnology companies or other pharmaceutical companies, including our competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment. Although we try to ensure that our employees do not use the intellectual property and other proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed such intellectual property, including trade secrets or other proprietary information. Litigation may be necessary to defend against these claims. We are not aware of any threatened or pending claims related to these matters or concerning the agreements with our senior management, but litigation may be necessary in the future to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants 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, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and scientific personnel.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We rely on trade secrets to protect our proprietary know-how and technological advances, especially where we have not filed a patent application or where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to protect our trade secrets and other proprietary information. However, any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets. Accordingly, these agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights. In addition, others may independently discover our trade secrets and

proprietary information. Further, the FDA, as part of its Transparency Initiative, a proposal by the FDA to increase disclosure and make data more accessible to the public, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all. Failure to obtain or maintain trade secret protection could enable competitors to use our proprietary information to develop products that compete with our products or cause additional, material adverse effects upon our competitive business position and financial results.

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

Any lawsuits relating to infringement of intellectual property rights brought by or against us will be costly and time consuming and may adversely impact the price of our common stock.

We may be required to initiate litigation to enforce or defend our intellectual property. These lawsuits can be very time consuming and costly. There is a substantial amount of litigation involving patent and other intellectual property rights in the pharmaceutical industry generally. Such litigation or proceedings could substantially increase our operating expenses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

In any infringement litigation, any award of monetary damages we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are resolved. Further, any claims we assert against a perceived infringer could provoke these parties to assert counterclaims against us alleging that we have infringed their patents. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

In addition, our patents and patent applications could face other challenges, such as interference proceedings, opposition proceedings, re-examination proceedings, and other forms of post-grant review. In the United States, for example, post-grant review has recently been expanded. Any of these challenges, if successful, could result in the invalidation of, or in a narrowing of the scope of, any of our patents and patent applications subject to challenge. Any of these challenges, regardless of their success, would likely be time consuming and expensive to defend and resolve and would divert our management and scientific personnel's time and attention.

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 material adverse effect on the market price of our common stock.

We will need to obtain FDA approval of any proposed product names, and any failure or delay associated with such approval may adversely affect our business.

Any name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the USPTO. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies certain medical claims or contributes to an overstatement of efficacy. If the FDA objects to any of our proposed product names, we may be required to adopt an alternative name for our product candidates. If we adopt an alternative name, we would lose the benefit of our existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation extending the terms of our patents and obtaining data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA regulatory approval for our product candidates, one or more of our U.S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five

years as compensation for patent term lost during product development and the FDA regulatory review process. Patent term restorations, however, cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval by the FDA.

The application for patent term extension is subject to approval by the USPTO, in conjunction with the FDA. It takes at least six months to obtain approval of the application for patent term extension. We may not be granted an extension 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 applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or 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 will be shortened and our competitors may obtain earlier approval of competing products, and our ability to generate revenues could be materially adversely affected.

Risks Related to Our Business Operations and Industry

We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.

We are currently a small company with twenty-four full-time employees as of March 1, 2017, and we outsource to consultants or other organizations a portion of our operations, including but not limited to research and development and conduct of clinical trials and certain administrative functions. In order to commercialize our product candidates, we will need to substantially increase our operations. We plan to continue to build our compliance, financial and operating infrastructure to ensure the maintenance of a well-managed company. We expect to significantly expand our employment base when we reach the full commercial stages of our current product candidates' life cycle.

Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our management, personnel and systems currently in place may not be adequate to support this future growth. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to:

- manage our clinical trials and the regulatory process effectively;
- manage the manufacturing of product candidates and potential products for clinical and commercial use;
- integrate current and additional management, administrative, financial and sales and marketing personnel;
- develop a marketing and sales infrastructure;
- hire new personnel necessary to effectively commercialize our product candidates;
- develop our administrative, accounting and management information systems and controls; and
- hire and train additional qualified personnel.

Product candidates that we may acquire or develop in the future may be intended for patient populations that are large. In order to continue development and marketing of these product candidates, if approved, we would need to significantly expand our operations. Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to manage successfully future market opportunities or our relationships with customers and other third parties. In particular, we will need to build out our finance, accounting and reporting infrastructure to meet our reporting obligations as a public company. Because we have never had this infrastructure, there may be increased risk that we will not be able to adequately meet these reporting obligations in a timely manner.

We are a clinical-stage company and it may be difficult for you to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of therapies for glaucoma. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, conducting research and developing our product candidates. We have not yet demonstrated our ability to successfully complete a pivotal Phase 3 clinical trial, obtain regulatory approval of a product candidate, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history and more experience with late stage development and commercialization of product candidates.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition from a company with a product development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We depend upon our key personnel and our ability to attract and retain employees.

Our future growth and success depend on our ability to recruit, retain, manage and motivate our employees. We are highly dependent on our senior management team and our scientific founders, as well as the other principal members of our management and scientific teams. Although we have formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time. The loss of the services of any member of our senior management or scientific team or the inability to hire or retain experienced management personnel could adversely affect our ability to execute our business plan and harm our operating results.

Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. In particular, the loss of David P. Southwell, our President and Chief Executive Officer, Rudolf A. Baumgartner, M.D., our Executive Vice President and Chief Medical Officer, or Dale Ritter, our Vice President—Finance, could be detrimental to us if we cannot recruit suitable replacements in a timely manner. We do not currently carry “key person” insurance on the lives of members of executive management. The competition for qualified personnel in the pharmaceutical field is intense. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel. 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 employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the Securities and Exchange Commission, or SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

If we engage in acquisitions or mergers in the future, we will incur a variety of costs and we may never realize the anticipated benefits of such acquisitions.

We may attempt to acquire companies, businesses, technologies, services, products or other product candidates or merge with other companies in the future that we believe are a strategic fit with our business. We have no present agreement regarding any material acquisitions or other transactions. However, if we do undertake any acquisitions or mergers, the process of integrating an acquired or merged business, technology, service, product candidates or potential products into our business may result in unforeseen operating difficulties and expenditures, including diversion of resources and management’s attention from our core business. In addition, we may fail to retain key executives and employees of acquired or merged companies, which may reduce the value of the acquisition or merger, or give rise to additional integration costs. Future acquisitions or mergers could result in additional issuances of equity securities that would dilute the ownership of existing stockholders. Future acquisitions or mergers could also result in the incurrence of debt, actual or contingent liabilities or the amortization of expenses related to other intangible assets, any of which could adversely affect our operating results. In addition, we may fail to realize the anticipated benefits of any acquisition or merger.

Our business is affected by macroeconomic conditions.

Various macroeconomic factors could adversely affect our business and the results of our operations and financial condition, including changes in inflation, interest rates and foreign currency exchange rates and overall economic conditions and uncertainties, including those resulting from current and future conditions in the global financial markets. For instance, if inflation or other factors were to significantly increase our business costs, it may not be feasible to pass through price increases to patients. Interest rates, the liquidity of the credit markets and the volatility of the capital markets could also affect the value of our investments and our ability to liquidate our investments in order to fund our operations.

Interest rates and the ability to access credit markets could also adversely affect the ability of patients, payors and distributors to purchase, pay for and effectively distribute our products. Similarly, these macroeconomic factors could affect the ability of our potential future contract manufacturers, sole-source or single-source suppliers or licensees to remain in business or otherwise manufacture or supply product. Failure by any of them to remain in business could affect our ability to manufacture products.

If product liability lawsuits are successfully brought against us, our insurance may be inadequate and we may incur substantial liability.

We face an inherent risk of product liability claims as a result of the clinical testing of our product candidates. We will face an even greater risk if we commercially sell our product candidates or any other potential products that we develop. We maintain product liability insurance with an aggregate limit of $10 million that cover our clinical trials and we plan to maintain insurance against product liability lawsuits for commercial sale of our product candidates. Historically, the potential liability associated with product liability lawsuits for pharmaceutical products has been unpredictable. Although we believe that our current insurance is a reasonable estimate of our potential liability and represents a commercially reasonable balancing of the level of coverage as compared to the cost of the insurance, we may be subject to claims in connection with our clinical trials and, in the future, commercial use of our product candidates, for which our insurance coverage may not be adequate, and the cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial.

For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- reduced resources of our management to pursue our business strategy;
- decreased demand for our product candidates or potential products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant costs to defend resulting litigation;
- diversion of management and scientific resources from our business operations;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any products that we may develop.

We will need to increase our insurance coverage if our product candidates receive marketing approval and we begin selling them. However, the product liability insurance we will need to obtain in connection with the commercial sales of our product candidates, if and when they receive regulatory approval, may be unavailable in meaningful amounts or at a reasonable cost. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, if and when they obtain regulatory approval, which could materially adversely affect our business, financial condition, results of operations, cash flows and prospects.

Additionally, we do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, employment practices liability, auto, property, workers' compensation, products liability and directors' and officers' insurance. We do not know, however, if we will be able to maintain insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would materially adversely affect our financial position, cash flows and results of operations.

Business interruptions could delay us in the process of developing our products and could disrupt our sales.

Our headquarters is located in Lexington, Massachusetts. We are vulnerable to natural disasters, such as severe storms and other events that could disrupt our business operations. We do not carry insurance for natural disasters and we may not carry sufficient business interruption insurance to compensate us for losses that may occur. Any losses or damages we incur could have a material adverse effect on our business operations.

Our business and operations would suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems, and those of our CROs and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our drug development programs. For example, the loss of clinical trial data from completed or ongoing or planned 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 and the further development of our product candidates could be delayed.

A breach of the Company's computer systems and networks could materially adversely affect the Company's business and financial condition.

Our business requires us, including some of our vendors, to use and store personally identifiable and other sensitive information, such as health and medical data, for employees and patients. The security measures put in place by the Company, and such vendors, cannot provide absolute security, and the Company and our vendors' information technology infrastructure may be vulnerable to criminal cyber-attacks or data security incidents due to employee error, malfeasance, or other vulnerabilities. The techniques used by criminals to obtain unauthorized access to sensitive data are increasing in sophistication and are often novel, or change frequently. Such attacks now often take the form of phishing, spear-phishing, and other forms of human engineering and impersonation. These attacks could target not only personally identifiable information of the Company's employees and patients but the Company's intellectual property, trade secrets (such as drug formulations), and other proprietary information. The Company may be unable to anticipate these techniques or implement adequate preventative measures. As a result, there is no guarantee that despite the Company's best efforts, the Company will not become the victim of such an attack in the future, that unauthorized parties will not gain access to sensitive data stored on the Company's systems or the systems of Company's vendors, or that any such incident will be discovered in a timely manner.

Any such incident could compromise the Company's or such vendors' networks, and the information stored by the Company or such vendors could be accessed, misused, shared publicly, corrupted, lost, held for ransom, or stolen, resulting in fraud, including wire fraud related to Company assets, corporate espionage, or other harm. Moreover, if a data security incident or breach affects the Company's systems or such vendors' systems or results in the unauthorized release of personally identifiable information, the Company's reputation could be materially harmed and the Company may be exposed to a risk of loss or litigation and possible liability, which could result in a material adverse effect on the Company's business, results of operations, and financial condition. In the event clinical or other medical data from patients enrolled in clinical trials is exposed to unauthorized persons, either by the Company or the Company's vendors, the Company could face challenges enrolling patients in future trials. The Company's insurance coverage may not cover or may be inadequate to cover the losses it could incur should the Company experience a major data security event.

Our employees, independent contractors, principal investigators, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading, which could significantly harm our business.

We are exposed to the risk of fraud or other misconduct by employees and independent contractors, such as principal investigators, consultants, commercial partners and vendors. Misconduct by these parties could include failures to comply with the regulations of the FDA and comparable non-U.S. regulatory authorities, provide accurate information to the FDA and comparable non-U.S. regulatory authorities, comply with fraud and abuse and other healthcare laws in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and other business arrangements in the healthcare industry are subject to extensive laws intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws may restrict or prohibit a wide range of business activities, including, but not limited to, research, manufacturing, distribution, pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We adopted a code of ethics, but it is not always possible to identify and deter employee and other third-party misconduct, and the precautions we take to detect and prevent this

activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws. If any such actions are instituted against us resulting from such misconduct those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate.

We and our development partners, third-party manufacturers and suppliers use biological materials and may use hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

We and our development partners, third-party manufacturers and suppliers may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety or the environment. Our operations and the operations of our third-party manufacturers and suppliers also produce hazardous waste products. Federal, state and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

The availability of our common stock and securities linked to our common stock for sale in the future could reduce the market price of our common stock.

In the future, we may issue equity and equity-linked securities to raise cash for acquisitions or otherwise. We may also acquire interests in other companies by using a combination of cash and our common stock or just our common stock. We may also issue preferred stock or additional securities convertible into our common stock or preferred stock. Any of these events may dilute your ownership interest in our company and have an adverse effect on the price of our common stock.

Risks Related to Ownership of Our Common Stock

If we fail to maintain the listing of our common stock with a U.S. national securities exchange, the liquidity of our common stock could be adversely affected.

If our common stock is delisted by NASDAQ, our common stock may be eligible to trade on the OTC Bulletin Board or another over-the-counter market. Any such alternative would likely result in it being more difficult for us to raise additional capital through the public or private sale of equity securities and for investors to dispose of, or obtain accurate quotations as to the market value of, our common stock. In addition, there can be no assurance that our common stock would be eligible for trading on any such alternative exchange or markets.

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above your purchase price of our shares.

Our initial public offering was completed in February 2015. Therefore, there has only been a public market for our common stock for a short period of time. Our common stock is listed on NASDAQ. Since shares of our common stock were sold in our initial public offering in February 2015 at $6.00 per share, our stock price has reached a high of $19.45 per share and a low of $1.50 per share through March 1, 2017.

The trading price of our common stock is likely to continue to be volatile, and you can lose all or part of your investment in us. In fact, following our announcement of the results of our Phase 3 monotherapy clinical trial on January 3, 2017, the price of our common stock dropped $4.35 per share, or 71%, from $6.10 per share as of the close of business on December 30, 2016, to $1.75 per share as of the close of business on January 3, 3017. The following factors, in addition to other factors described in this “Risk Factors” section and elsewhere in this Annual Report on Form 10-K for the fiscal year ended December 31, 2016, may have a significant impact on the market price of our common stock:

- announcements of regulatory approval or a complete response letter, or specific label indications or patient populations for its use, or changes or delays in the regulatory review process;
- announcements of therapeutic innovations or new products by us or our competitors;

- adverse actions taken by regulatory agencies with respect to our clinical trials, manufacturing supply chain or sales and marketing activities;
- any adverse changes to our relationship with manufacturers or suppliers;
- the results of our testing and clinical trials;
- the results of our efforts to acquire or license additional product candidates;
- variations in the level of expenses related to our existing product candidates or preclinical and clinical development programs;
- any intellectual property infringement actions in which we may become involved;
- announcements concerning our competitors or the pharmaceutical industry in general;
- achievement of expected product sales and profitability;
- manufacture, supply or distribution shortages;
- actual or anticipated fluctuations in our quarterly or annual operating results;
- changes in financial estimates or recommendations by securities analysts;
- trading volume of our common stock;
- sales of our common stock by us, our executive officers and directors or our stockholders in the future;
- sales by us of securities linked to our common stock;
- general economic and market conditions and overall fluctuations in the U.S. equity markets;
- changes in accounting principles; and
- the loss of any of our key scientific or management personnel.

In addition, the stock market, in general, and small pharmaceutical and biotechnology companies have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. Further, a significant decline in the financial markets and other related factors beyond our control may cause our stock price to decline rapidly and unexpectedly.

We and our management are parties to a lawsuit which, if adversely decided against, could adversely affect our business and cause the price of our common stock to continue to decrease. We may also be subject to other securities litigation in the future, which is expensive and could divert management attention.

Our share price has been and may continue to be volatile, and in the past companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. This risk is especially relevant for us because our stock price declined following our announcement of top-line data from our Phase 3 clinical trial of *trabodenoson* for the treatment of primary open-angle glaucoma or ocular hypertension. On January 6, 2017, a purported stockholder of the Company filed a putative class action in the U.S. District Court for the District of Massachusetts, against the Company, David Southwell, Rudolf Baumgartner, Dale Ritter, and William McVicar, captioned Whitehead v. Inotek Pharmaceuticals Corporation, et al., No. 1:17-cv-10025. The complaint alleges violations of Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 and SEC Rule 10b-5 based on allegedly false and misleading statements and omissions regarding our MATrX-1 Phase 3 clinical trial of *trabodenoson*. The lawsuit seeks among other things, unspecified compensatory damages, interest, attorneys' fees and costs, and unspecified equitable/injunctive relief. The Company will vigorously defend plaintiff's claims on the factual record, which it believes will prove that the Company is not liable to the plaintiff in any regard. This litigation or future litigation of this type could result in substantial costs and diversion of management's attention and resources, which could adversely impact our business. Any adverse determination in this or future litigation could also subject us to significant liabilities.

Our existing principal stockholders, executive officers and directors own a significant percentage of our common stock and will be able to exert a significant control over matters submitted to our stockholders for approval.

As of February 15, 2017, our officers and directors, and stockholders who individually own more than 5% of our outstanding common stock, in the aggregate, beneficially owned approximately 44% of our common stock.

This significant concentration of share ownership may adversely affect the trading price for our common stock because investors often perceive disadvantages in owning stock in companies with controlling stockholders. As a result, these stockholders, if they acted together, could significantly influence all matters requiring approval by our stockholders, including the election of directors and the approval of mergers or other business combination transactions. These stockholders may be able to determine all matters requiring stockholder approval. The interests of these stockholders may not always coincide with our interests or the interests of other stockholders or noteholders. This may also prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as a stockholder or noteholder, and they may act in a manner that advances their best interests and not necessarily those of other stockholders or noteholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock and 2021 Convertible Notes.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock or any of our securities linked to our common stock, or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities or equity-linked securities. As of December 31, 2016, we have 26,986,318 outstanding shares of common stock, which excludes 6,483,791 shares of common stock issuable upon conversion of the 2021 Convertible Notes, 2,675,458 shares of common stock issuable upon the exercise of stock options outstanding and exercisable at a weighted-average exercise price of $6.30 per share and 470,000 unvested Restricted Stock Units outstanding as of December 31, 2016.

If securities or industry analysts do not publish or cease publishing research or reports about us, our business or our market, or if they adversely change their recommendations or publish negative reports regarding our business or our stock, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts may publish about us, our business, our market or our competitors. We do not have any control over these analysts and we cannot provide any assurance that analysts will cover us or provide favorable coverage. If any of the analysts who may cover us adversely change their recommendation regarding our stock, or provide more favorable relative recommendations about our competitors, our stock price could decline. If any analyst who may cover us were to cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Because we do not intend to declare cash dividends on our shares of common stock in the foreseeable future, stockholders must rely on appreciation of the value of our common stock for any return on their investment.

We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, we expect that only appreciation of the price of our common stock, if any, will provide a return to holders of our common stock for the foreseeable future.

If we are unable to substantially utilize our net operating loss carryforward, our financial results will be adversely affected.

As of December 31, 2016 we had federal and state net operating losses of approximately $105.3 million and $62.7 million, respectively, which may be utilized against future federal and state income taxes, respectively. In general, a corporation that undergoes an “ownership change” is subject to limitations on its ability to utilize its pre-change net operating losses, or NOLs, to offset future taxable income. In general, an ownership change occurs if the aggregate stock ownership of certain stockholders (generally 5% stockholders, applying certain look-through and aggregation rules) increases by more than fifty percentage points over such stockholders’ lowest percentage ownership during the testing period (generally three years). Purchases of our common stock in amounts greater than specified levels, which are beyond our control, or prior issuances of our common stock, could create a limitation on our ability to utilize our NOLs for tax purposes in the future. Limitations imposed on our ability to utilize NOLs could cause federal and state income taxes to be paid earlier than would be paid if such limitations were not in effect and could cause such NOLs to expire unused, in each case reducing or eliminating the benefit of such NOLs. Furthermore, we may not be able to generate sufficient taxable income to utilize our NOLs before they expire. If any of these events occur, or have occurred in the past, we may not derive some or all of the expected benefits from our NOLs. We have determined that we have experienced prior ownership changes occurring in 2005, 2007, and 2015. NOLs generated prior to these changes, although subject to an annual limitation, can be utilized in future years as well as any post change NOLs. In addition, at the state level there may be periods during which the use of NOLs is suspended or otherwise limited, which would accelerate or may permanently increase state taxes owed.

The requirements associated with being a public company require significant company resources and management attention.

We are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, the listing requirements of the securities exchange on which our common stock is traded and other applicable securities rules and regulations. The Exchange Act requires that we file annual, quarterly and current reports with respect to our business and financial condition and maintain effective disclosure controls and procedures and internal control over financial reporting. In addition, subsequent rules implemented by the SEC and NASDAQ may also impose various additional requirements on public companies. As a result, we incur substantial legal, accounting and other expenses. Further, the corporate infrastructure demanded of a public company may divert management's attention from implementing our growth strategy. We have made, and will continue to make, changes to our corporate governance standards, disclosure controls and financial reporting and accounting systems to meet our reporting obligations. However, the measures we take may not be sufficient to satisfy our obligations as a public company, which could subject us to delisting of our common stock, fines, sanctions and other regulatory action and potentially civil litigation.

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

Now that we are a public company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and The NASDAQ Stock Market have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

The JOBS Act will allow us to postpone the date by which we must comply with some of the laws and regulations intended to protect investors and to reduce the amount of information we provide in our reports filed with the SEC, which could undermine investor confidence in our company and adversely affect the market price of our common stock.

For so long as we remain an "emerging growth company" as defined in the JOBS Act, we may take advantage of certain exemptions from various requirements that are applicable to public companies that are not "emerging growth companies" including:

- the provisions of Section 404(b) of the Sarbanes-Oxley Act requiring that our independent registered public accounting firm provide an attestation report on the effectiveness of our internal control over financial reporting;
- the "say on pay" provisions (requiring a non-binding stockholder vote to approve compensation of certain executive officers) and the "say on golden parachute" provisions (requiring a non-binding stockholder vote to approve golden parachute arrangements for certain executive officers in connection with mergers and certain other business combinations) of the Dodd-Frank Wall Street Reform and Consumer Protection Act, or Dodd-Frank Act, and some of the disclosure requirements of the Dodd-Frank Act relating to compensation of its chief executive officer;
- the requirement to provide detailed compensation discussion and analysis in proxy statements and reports filed under the Exchange Act, and instead provide a reduced level of disclosure concerning executive compensation; and
- any rules that may be adopted by the Public Company Accounting Oversight Board requiring mandatory audit firm rotation or a supplement to the auditor's report on the financial statements.

We may take advantage of these exemptions until we are no longer an "emerging growth company." We would cease to be an "emerging growth company" upon the earliest of: (i) December 31, 2020; (ii) the last day of the first fiscal year in which our annual gross revenues are $1 billion or more; (iii) the date on which we have, during the previous three-year period, issued more than $1

billion in non-convertible debt securities; or (iv) as of the end of any fiscal year in which the market value of our common stock held by non-affiliates exceeded $700 million as of the end of the second quarter of that fiscal year.

Although we are still evaluating the JOBS Act, we currently intend to take advantage of some, but not all, of the reduced regulatory and reporting requirements that will be available to us so long as we qualify as an "emerging growth company." For example, we have irrevocably elected under Section 107 of the JOBS Act not to take advantage of the extension of time to comply with new or revised financial accounting standards available under Section 102(b) of the JOBS Act. Our independent registered public accounting firm will not be required to provide an attestation report on the effectiveness of our internal control over financial reporting so long as we qualify as an "emerging growth company," which may increase the risk that weaknesses or deficiencies in our internal control over financial reporting go undetected. Likewise, so long as we qualify as an "emerging growth company," we may elect not to provide you with certain information, including certain financial information and certain information regarding compensation of our executive officers, that we would otherwise have been required to provide in filings we make with the SEC, which may make it more difficult for investors and securities analysts to evaluate our company. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock, and our stock price may be more volatile and may decline.

Some provisions of our charter document, Delaware law and the indenture that governs our 2021 Convertible Notes may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our amended and restated certificate of incorporation and our bylaws as well as provisions of the Delaware General Corporation Law, or DGCL, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders, including transactions in which stockholders might otherwise receive a premium for their shares. These provisions include:

- establishing a classified board of directors such that not all members of the board are elected at one time;
- allowing the authorized number of our directors to be changed only by resolution of our board of directors;
- limiting the removal of directors by the stockholders;
- authorizing the issuance of "blank check" preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders;
- eliminating the ability of stockholders to call a special meeting of stockholders;
- establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings; and
- requiring 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 our bylaws.

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, which is responsible for appointing the members of our management. In addition, we are subject to Section 203 of the DGCL, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with an interested stockholder for a period of three years following the date on which the stockholder became an interested stockholder, unless such transactions are approved by our board of directors. This provision could have the effect of delaying or preventing a change of control, whether or not it is desired by or beneficial to our stockholders.

In addition, the terms of our 2021 Convertible Notes require us to repurchase the 2021 Convertible Notes in cash in the event of a fundamental change. A takeover of our company, if such takeover constituted a "fundamental change," would trigger an option of the holders of the 2021 Convertible Notes to require us to repurchase the 2021 Convertible Notes. This may have the effect of delaying or preventing a takeover of our company that would otherwise be beneficial to investors in the 2021 Convertible Notes.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters is located in Lexington, Massachusetts, and consists of approximately 15,000 square feet of leased office space under a lease that expires in February 2023.

Item 3. Legal Proceedings

On January 6, 2017, a purported stockholder of the Company filed a putative class action in the U.S. District Court for the District of Massachusetts, against the Company, David Southwell, Rudolf Baumgartner, Dale Ritter, and William McVicar, captioned *Whitehead v. Inotek Pharmaceuticals Corporation, et al.*, No. 1:17-cv-10025. The complaint alleges violations of Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 and SEC Rule 10b-5 based on allegedly false and misleading statements and omissions regarding our MATrX-1 phase 3 clinical trial of trabodenoson. The lawsuit seeks among other things, unspecified compensatory damages, interest, attorneys' fees and costs, and unspecified equitable/injunctive relief.

From time to time, we may be subject to other various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, we do not believe we are party to any other claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

On February 18, 2015, our common stock began trading on the Nasdaq Global Select Market under the symbol "ITEK". Prior to that time, there was no public market for our common stock. Shares sold in our initial public offering were priced at $6.00 per share. The following table shows the high and low prices per share of our common stock as reported on the Nasdaq Global Select Market for the period indicated:

2015	High	Low
February 18, 2015 to March 31, 2015 (First Quarter)	$ 6.20	$ 5.05
Second Quarter	$ 6.14	$ 4.68
Third Quarter	$ 19.45	$ 4.71
Fourth Quarter	$ 13.36	$ 9.01

2016	High	Low
First Quarter	$ 11.89	$ 5.81
Second Quarter	$ 10.90	$ 6.60
Third Quarter	$ 9.90	$ 6.42
Fourth Quarter	$ 9.60	$ 5.85

On March 6, 2017, the closing price for our common stock as reported on the NASDAQ Global Market was $1.55.

Stockholders

As of March 6, 2017, there were 35 stockholders of record, which excludes stockholders whose shares were held in nominee or street name by brokers.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay cash dividends will be made at the discretion of our board of directors. In addition, the terms of our outstanding indebtedness restrict our ability to pay cash dividends, and any future indebtedness that we may incur could preclude us from paying cash dividends. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Securities authorized for issuance under equity compensation plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

We deemed the grants and exercises of stock options described above to be exempt from registration under the Securities Act in reliance on Rule 701 of the Securities Act as offers and sales of securities under compensatory benefit plans and contracts relating to compensation in compliance with Rule 701. Each of the recipients of securities in any transaction exempt from registration either received or had adequate access, through employment, business or other relationships, to information about us.

Use of Proceeds from Registered Securities

In April 2016, we filed a registration statement on Form S-3 containing two prospectuses: (i) a base prospectus which covers the offering, issuance and sale by us of up to $200.0 million in the aggregate of an indeterminate number of shares of common stock and preferred stock, such indeterminate principal amount of debt securities and such indeterminate number of warrants and; and (ii) a sales agreement prospectus covering the offering, issuance and sale by us of up to a maximum aggregate offering price of $50.0 million of our common stock that may be issued and sold under an at-the-market sales agreement with Cowen and Company, LLC, or the ATM. The $50.0 million of common stock that may be issued and sold under the ATM reduces the available balance under the base

prospectus by the amount issued. During the year ended December 31, 2016, we sold 482,689 shares of common stock and received net proceeds of $4.0 million pursuant to the ATM. We are using the net proceeds from this offering primarily for research, development, manufacturing, and general and administrative expenses, and for other general corporate purposes.

In August 2016, we filed a prospectus supplement to our Form S-3 pursuant to which we closed an underwritten public offering of $52.0 million aggregate principal amount of 5.75% Convertible Senior Notes due 2021, including $2.0 million from an exercise of the underwriters' overallotment option, or the 2021 Convertible Notes, and received net proceeds of approximately $48.7 million after deducting underwriting discounts and offering-related costs. We are using the net proceeds from this offering to fund the continued testing of *trabodenoson* as a monotherapy and as a fixed-dose combination with *latanoprost* for the reduction of IOP and for general corporate purposes.

Issuer Purchases of Equity Securities

There were no repurchases of shares of common stock made during the year ended December 31, 2016.

Item 6. Selected Financial Data

We derived the selected consolidated statements of operations data for the years ended December 31, 2016 and 2015 and the consolidated balance sheet data as of December 31, 2016 and 2015 from our audited consolidated financial statements appearing elsewhere in this annual report on Form 10-K.

The selected consolidated financial data should be read in conjunction with Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the consolidated financial statements and the notes thereto included elsewhere in this report. The selected consolidated financial data in this section are not intended to replace our consolidated financial statements and the related notes. Our historical results are not necessarily indicative of our future results.

	For the Years Ended December 31,	
(in thousands, except share and per share data)	**2016**	**2015**
Consolidated Statements of Operations Data:		
Operating expenses:		
Research and development	$ (31,985)	$ (12,554)
General and administrative	(9,894)	(7,842)
Loss from operations	(41,879)	(20,396)
Interest expense	(1,418)	(1,230)
Interest income	443	89
Loss on extinguishment of debt	-	(4,399)
Change in fair value of warrant liabilities	-	267
Change in fair value of Convertible Bridge Notes redemption rights derivative	-	480
Change in fair value of 2020 Convertible Notes derivative liability	-	(42,793)
Net loss	$ (42,854)	$ (67,982)
Net loss per common share—basic and diluted	$ (1.60)	$ (3.72)
Weighted-average common shares outstanding—basic and diluted	26,735,175	18,311,333

	December 31,	
(in thousands)	**2016**	**2015**
Consolidated Balance Sheet Data:		
Cash and cash equivalents	$ 29,798	$ 80,042
Short-term investments	96,675	31,238
Total assets	129,647	113,321
Convertible notes payable	48,960	—
Total liabilities	56,479	4,508
Accumulated deficit	(238,877)	(196,023)
Total stockholders' equity	73,168	108,813

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 in conjunction with our "Selected Financial Data" and our consolidated financial statements, related notes and other financial information included elsewhere in this Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties such as our plans, objectives, expectations and intentions. Our actual results could differ materially from those discussed in these forward looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified below and those discussed in "Risk Factors" included elsewhere in this prospectus.

Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of therapies for glaucoma. Glaucoma is a disease of the eye that is typically characterized by structural evidence of optic nerve damage, vision loss and consistently elevated intraocular pressure ("IOP"). Our lead product candidate, *trabodenoson*, is a first-in-class selective adenosine mimetic that we rationally designed to lower IOP by restoring the eye's natural pressure control mechanism. Our product pipeline includes *trabodenoson* monotherapy delivered in an eye drop formulation, as well as a fixed-dose combination ("FDC") of *trabodenoson* with *latanoprost*, a prostaglandin analogue ("PGA"), given once-daily. Our completed Phase 2 trial of *trabodenoson* co-administered with *latanoprost* demonstrated IOP-lowering in patients who have previously had inadequate response to *latanoprost*. These patients represent PGA poor-responders, as evidenced by persistently elevated IOP at levels that typically require the addition of a second drug to further lower IOP.

On January 3, 3017, we announced top-line results of MATrX-1, the first pivotal Phase 3 trial of *trabodenoson* for the treatment of primary open-angle glaucoma or ocular hypertension. The trial did not meet its primary endpoint because it did not demonstrate a statistically significant difference in absolute intraocular pressure ("IOP"), from placebo at every single one of the 12 time points comprising the primary endpoint. This was due to a larger than expected treatment effect in the placebo/vehicle group, as compared to both our prior Phase 2 data and a recent meta-analysis examining placebo responses from 10 placebo-controlled trials, which showed a placebo/vehicle result of -2.01 mmHg (Raber, et al). During analysis of the IOP data from the trial, a treatment-by-site interaction was found where a small number of sites (4 sites out of a total of 55) caused an important change in the expected vehicle results. MATrX-1 did achieve several clinically meaningful secondary endpoints - the 6% dose was significant versus placebo in the daily IOP change from diurnal baseline at all days tested. Additionally, an analysis of responders (subjects with IOP reduction of 5mmHg or greater from baseline) indicated a statistically higher proportion of responders in the 6% *trabodenoson* group than the placebo group at all visits. There were no significant safety or tolerability events reported. The safety profile of *trabodenoson* was comparable to placebo and there was minimal drug related hyperemia.

In August 2016, we closed an underwritten public offering of $52.0 million aggregate principal amount of 5.75% Convertible Senior Notes due 2021, including $2.0 million from an exercise of the underwriters' overallotment option, (the "2021 Convertible Notes"), and received net proceeds of approximately $48.7 million after deducting underwriting discounts and offering-related costs. (See Note 5 in the accompanying notes to the consolidated financial statements).

In July 2016, we announced the initiation of a Phase 2 dose-ranging trial of a fixed-dose combination ("FDC") of *trabodenoson* and *latanoprost*. The trial will enroll approximately 165 patients with an IOP greater than or equal to 25 mmHg and less than or equal to 34 mmHg; which represents the patients most likely to receive treatment for glaucoma or ocular hypertension. Data from this trial is expected in mid-2017.

In April 2016, we filed a registration statement on Form S-3 containing two prospectuses: (i) a base prospectus which covers the offering, issuance and sale by us of up to $200.0 million in the aggregate of an indeterminate number of shares of common stock and preferred stock, such indeterminate principal amount of debt securities and such indeterminate number of warrants and; and (ii) a sales agreement prospectus covering the offering, issuance and sale by us of up to a maximum aggregate offering price of $50.0 million of our common stock that may be issued and sold under an at-the-market sales agreement with Cowen and Company, LLC (the "ATM"). The $50.0 million of common stock that may be issued and sold under the ATM reduces the available balance under the base prospectus by the amount issued. During the year ended December 31, 2016, we sold 482,689 shares of common stock and received net proceeds of $4.0 million pursuant to the ATM. At December 31, 2016, $45.6 million was available for sale of common stock under the ATM.

As disclosed in Item 5.02 of the Current Report on Form 8-K filed with the Securities and Exchange Commission ("SEC") on October 7, 2016, we informed William McVicar, Ph.D. that his employment would be ending. Dr. McVicar stepped down from his position as our Executive Vice President, Chief Scientific Officer and executive officer effective October 4, 2016. Dr. McVicar has agreed to remain employed by us in a non-executive capacity as Senior Advisor, through April 4, 2017, unless we terminate him or he resigns sooner (such date, the "Separation Date"), to facilitate a smooth transition. In connection with the departure, we and Dr. McVicar have entered into a Transition Agreement signed on October 27, 2016 (the "Transition Agreement"), effective as of November 3, 2016. (See Note 9 of Notes to Consolidated Financial Statements.)

As of December 31, 2016, we had an accumulated deficit of $238.9 million and cash and cash equivalents and short-term investments aggregating $126.5 million. We estimate we have sufficient funding to sustain operations into 2019. See “Liquidity and Capital Resources.”

Since our inception on July 7, 1999, we have devoted substantially all of our resources to business planning, raising capital, product research and development, applying for and obtaining government and private grants, recruiting management, research and technical staff and other personnel, acquiring operating assets, and undertaking preclinical studies and clinical trials of our lead product candidates. We have not completed development of any product candidate and we have therefore not generated any revenues from product sales.

Factors Affecting our Results of Operations

We do not expect our expenses to increase in 2017 as we fully assess the results from the latest Phase 3 trial. Results from our ongoing Phase 2 trial with our FDC product candidate are expected in mid-2017. If we successfully develop and launch *trabodenoson* as a monotherapy or any other product candidates, we expect to incur significant commercialization expenses related to sales, marketing, manufacturing and distribution of our products.

We will need to obtain additional funding in connection with our continuing operations. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or any potential future commercialization efforts. We will need to generate significant revenues to achieve profitability, and we may never do so. As a result, we expect to incur significant expenses and increasing operating losses for the foreseeable future.

Financial Overview

Revenue

We have not generated any revenue from product sales since our inception and do not expect to generate any revenue from the sale of products in the near future. Our ability to generate revenues will depend on the successful development, regulatory approval and commercialization of *trabodenoson* and any other future product candidates.

Research and Development Expenses

Research and development expenses consist primarily of the costs associated with our research and development activities, conducting preclinical studies and clinical trials and activities related to regulatory filings. Our research and development expenses consist of:

- direct clinical and non-clinical expenses which include expenses incurred under agreements with contract research organizations (“CROs”), contract manufacturing organizations, clinical sites and costs associated with preclinical activities and development activities and costs associated with regulatory activities;
- employee and consultant-related expenses, including compensation, benefits, travel and stock-based compensation expense for research and development personnel as well as consultants that conduct and support clinical trials and preclinical studies; and
- facilities and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies used in research and development activities.

We expense research and development costs as incurred. We record costs for some development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as subject enrollment, clinical site activations or other information our vendors provide to us.

The following table summarizes our research and development expenses by type of activity for the years ended December 31, 2016 and 2015:

(in thousands)	For the Years Ended December 31, 2016	2015
Trabodenoson—direct clinical and non-clinical	$ 22,598	$ 8,653
Personnel and other expenses:		
Employee and consultant-related expenses	7,763	3,483
Target validation expenses	802	—
Facility expenses	533	336
Other expenses	289	82
Total personnel and other expenses	9,387	3,901
Total research and development expenses	$ 31,985	$ 12,554

We do not track *trabodenoson*-related expenses by product candidate. All expenses related to *trabodenoson* as a monotherapy also benefit the FDC product candidate *trabodenoson* with *latanoprost*. We have expended approximately $74 million for external development costs related to *trabodenoson* from inception through December 31, 2016.

The process of conducting the necessary clinical research to obtain regulatory approval is costly and time consuming and the successful development of our product candidates is highly uncertain, especially considering the MATrX-1 Phase 3 clinical trial's failure to meet its primary endpoint. Our future research and development expenses will depend on the clinical success of our product candidates, as well as ongoing assessments of the commercial potential of such product candidates. In addition, we cannot forecast with any degree of certainty which product candidates may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements. We do not expect our research and development expenses to increase in 2017 as we fully assess the results from the latest Phase 3 trial.

The successful development and commercialization of our 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 efficacy and potential advantages of our product candidates compared to alternative treatments, including any standard of care;
- the market acceptance of our product candidates;
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- significant and changing government regulation; and
- the timing, receipt and terms of any marketing approvals.

A change in the outcome of any of these variables with respect to the development of *trabodenoson* or any other product candidate that we may develop could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials or other testing beyond those that we currently contemplate for the completion of clinical development of *trabodenoson* or any other product candidate that we may develop 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.

As a result of the uncertainties discussed above, we are unable to determine with certainty the duration and completion costs of our development programs or precisely when and to what extent we will receive revenue from the commercialization and sale of our product candidates. We may never succeed in achieving regulatory approval for one or more of our product candidates. The duration, costs and timing of clinical trials and development of any product candidates will depend on a variety of factors, including the uncertainties of future preclinical studies and clinical trials, uncertainties in the clinical trial enrollment rate and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including efficacy and tolerability profiles, manufacturing capability, competition, and commercial viability.

General and Administrative Expenses

General and administrative expenses consist of salaries and related benefit costs, including stock-based compensation for administrative personnel. Other significant general and administrative expenses include professional fees for legal, patents, consulting,

investor and public relations, auditing and tax services as well as other direct and allocated expenses for rent and maintenance of facilities, insurance and other supplies used in general and administrative activities.

Interest Expense

Interest expense in 2016 relates to our 2021 Convertible Notes which are due in August 2021. In 2015 and prior, interest expense related to our 2020 Convertible Notes, notes payable, convertible promissory notes, amortization of loan discounts as well as interest calculated based on the amortization of the beneficial conversion feature of the convertible promissory notes. In February 2015, we repaid our borrowings under our existing notes payable agreements with Horizon Technology Finance Corporation and Fortress Credit Co. LLC with the proceeds from our IPO and the convertible promissory notes converted into common stock pursuant to the IPO. In July and August of 2015 our 2020 Convertible Notes fully converted into common stock.

Interest Income

Interest income relates to interest earned from invested funds.

Results of Operations

Comparison of the Years Ended December 31, 2016 and 2015

The following table summarizes the results of our operations for the years ended December 31, 2016 and 2015:

(in thousands)	For the Years Ended December 31, 2016	2015	Increase (Decrease)
Operating expenses:			
Research and development	$ (31,985)	$ (12,554)	$ 19,431
General and administrative	(9,894)	(7,842)	2,052
Loss from operations	(41,879)	(20,396)	21,483
Interest expense	(1,418)	(1,230)	188
Interest income	443	89	(354)
Loss on extinguishment of debt	-	(4,399)	(4,399)
Change in fair value of warrant liabilities	-	267	267
Change in fair value of derivative liabilities	-	(42,313)	(42,313)
Net loss	$ (42,854)	$ (67,982)	$ (25,128)

Loss from operations

Loss from operations increased $21.5 million to $41.9 million for the year ended December 31, 2016, as compared to $20.4 million for the year ended December 31, 2015, and related primarily to the $19.4 million increase in research and development expenses.

Research and development expenses

Research and development expenses increased $19.4 million to $32.0 million for the year ended December 31, 2016, as compared to $12.6 million for the year ended December 31, 2015. This increase primarily reflects $12.1 million of increased clinical expenses related to our Phase 3 trial with monotherapy that was ongoing for the full year and our Phase 2 trial with our FDC product candidate that commenced in October 2016. In 2016, we recorded a charge of $0.9 million relating to the termination of our Chief Scientific Officer. Additionally, employee-related expenses due to increased headcount and additional stock option grants increased $2.7 million, preclinical expenses increased $2.6 million and consulting expenses increased $0.7 million.

General and administrative expenses

General and administrative expenses increased $2.1 million to $9.9 million for the year ended December 31, 2016, as compared to $7.8 million for the year ended December 31, 2015. This increase primarily reflects $0.8 million related to increased staffing expenses due to increased headcount and salaries and $1.4 million primarily related to increased consulting and other outside services. Stock-based compensation expense decreased $0.2 million due to a one-time charge of $1.0 million in 2015 related to the elimination of repurchase rights and final vesting related to the Series X preferred shares held by our former CEO and CFO pursuant to our IPO, partially offset by higher stock compensation expense in 2016 due to increased headcount.

Interest expense

Interest expense increased $0.2 million, to $1.4 million, for the year ended December 31, 2016, as compared to $1.2 million for the year ended December 31, 2015. Interest expense in 2016 related to coupon interest and amortization of our debt discount and debt issuance costs related to our 2021 Convertible Notes. Interest expense in 2015 was comprised of $1.0 million for coupon interest and amortization of debt discount and deferred financing costs related to our 2020 Convertible Notes, $0.1 million related to our Convertible Bridge Notes and $0.1 million related to our notes payable.

Interest income

Interest income increased $0.3 million to $0.4 million for the year ended December 31, 2016, as compared to $0.1 million for the year ended December 31, 2015. This increase primarily reflects higher weighted average invested balances and interest rates.

Loss on extinguishment of debt

The loss on extinguishment of debt of $4.4 million in the year ended December 31, 2015, consisted of $3.7 million related to the July and August 2015 conversion of all of the 2020 Convertible Notes into common stock (see Note 5 in the accompanying notes to the consolidated financial statements), $0.4 million of unamortized debt discount and issuance costs related to our Convertible Bridge Notes and $0.3 million related to unamortized debt discount and issuance costs and prepayment fees related to our Notes Payable.

Change in fair value of warrant liabilities

The change in fair value of warrant liabilities for the year ended December 31, 2015, was a gain of $0.3 million related to a decrease in our warrant liabilities related to warrants to purchase shares of Series AA Preferred Stock that became warrants to purchase shares of common stock upon our IPO. There were no liability-classified warrants outstanding in 2016.

Change in fair value of derivative liabilities

The change in fair value of derivative liabilities for the year ended December 31, 2015, was a net loss of $42.3 million. We recorded a loss of $42.8 million in the year ended December 31, 2015, related to the final mark-to market of the 2020 Convertible Notes derivative liability in connection with the July and August 2015 full conversion of the 2020 Convertible Notes into common stock (see Note 5 in the accompanying notes to the consolidated financial statements), and a gain of $0.5 million related to the decrease in the value of the Convertible Bridge Notes redemption rights derivative.

Comparison of the Years Ended December 31, 2015 and 2014

The following table summarizes the results of our operations for the years ended December 31, 2015 and 2014:

(in thousands)	For the Years Ended December 31, 2015	2014	Increase (Decrease)
Operating expenses:			
Research and development	$ (12,554)	$ (5,592)	$ 6,962
General and administrative	(7,842)	(2,112)	5,730
Loss from operations	(20,396)	(7,704)	12,692
Interest expense	(1,230)	(980)	250
Interest income	89	—	(89)
Loss on extinguishment of debt	(4,399)	—	4,399
Change in fair value of warrant liabilities	267	(845)	(1,112)
Change in fair value of derivative liabilities	(42,313)	(2)	42,311
Net loss	$ (67,982)	$ (9,531)	$ 58,451

Research and development expenses

Research and development expenses increased $7.0 million to $12.6 million for the year ended December 31, 2015, from $5.6 million for the year ended December 31, 2014. This increase was related to higher pre-clinical expenses of $4.7 million primarily related to work preparing drug product for our *trabodenoson* clinical trials, along with ongoing pre-clinical studies, higher payroll-related and stock-based compensation expense of $1.9 million related to increased staffing and higher consulting expenses of $0.6

million. This increase was partially offset by a $0.3 million net reduction in direct clinical trial expenses as a result of the completion of our Phase 2 trial in October 2014 over increased costs of our Phase 3 trial that commenced in October 2015.

General and administrative expenses

General and administrative expenses increased $5.7 million, to $7.8 million, for the year ended December 31, 2015, as compared to $2.1 million for the year ended December 31, 2014. This increase included $1.6 million in stock-based compensation of which $1.0 million related to the elimination of repurchase rights and final vesting related to the Series X preferred shares held by our former CEO and CFO pursuant to our IPO. The remaining increase was due primarily to higher compensation-related expenses of $2.0 million primarily related to increased staffing, including our current CEO and VP of Finance, higher insurance expenses and other public-company related expenses of $0.9 million, higher professional fees of $0.7 million, and higher consulting fees of $0.3 million.

Interest expense

Interest expense increased $0.2 million, to $1.2 million, for the year ended December 31, 2015, as compared to $1.0 million for the year ended December 31, 2014. Interest expense in 2015 was comprised of $1.0 million for coupon interest and amortization of debt discount and deferred financing costs related to our 2020 Convertible Notes, $0.1 million related to our Convertible Bridge Notes and $0.1 million related to our notes payable. Interest expense in 2014 related primarily to our Notes Payable.

Loss on extinguishment of debt

The loss on extinguishment of debt of $4.4 million in the year ended December 31, 2015, consisted of $3.7 million related to the July and August 2015 conversion of all of the 2020 Convertible Notes into common stock (see Note 5 in the accompanying notes to the consolidated financial statements), $0.4 million of unamortized debt discount and issuance costs related to our Convertible Bridge Notes and $0.3 million related to unamortized debt discount and issuance costs and prepayment fees related to our Notes Payable.

Change in fair value of warrant liabilities

The change in fair value of warrant liabilities for the year ended December 31, 2015, was a gain of $0.3 million related to a decrease in our warrant liabilities related to warrants to purchase shares of Series AA Preferred Stock that became warrants to purchase shares of common stock upon our IPO. The $0.8 million loss in the year ended December 31, 2014, related to an increase in the value of the warrant liabilities related to our Series AA Preferred Stock.

Change in fair value of derivative liabilities

The change in fair value of derivative liabilities for the year ended December 31, 2015, was a net loss of $42.3 million. We recorded a loss of $42.8 million in the year ended December 31, 2015, related to the final mark-to market of the 2020 Convertible Notes derivative liability in connection with the July and August 2015 full conversion of the 2020 Convertible Notes into common stock (see Note 5 in the accompanying notes to the consolidated financial statements), and a gain of $0.5 million related to the decrease in the value of the Convertible Bridge Notes redemption rights derivative.

Liquidity and Capital Resources

Since inception, we have incurred accumulated net losses and negative cash flows from our operations. We incurred net losses of $42.9 million and $68.0 million for the years ended December 31, 2016 and 2015, respectively. Our operating activities used $37.3 million and $17.4 million during the years ended December 2016 and 2015, respectively. As of December 31, 2016, the Company had $126.5 million of cash and cash equivalents and short term investments. We estimate we have sufficient funding to sustain operations into 2019.

On August 5, 2016, we closed an underwritten public offering of $52.0 million aggregate principal amount of the 2021 Convertible Note, and received net proceeds of approximately $48.7 million after deducting underwriting discounts and offering-related costs. (See Note 5 in the accompanying notes to the consolidated financial statements).

During the year ended December 31, 2016, we sold 482,689 shares of common stock and received net proceeds of $4.0 million pursuant to the ATM. At December 31, 2016, $45.6 million was available for sale of common stock under the ATM.

In August 2015, we completed the Follow-on Offering, issuing 6,210,000 shares of our common stock resulting in aggregate net proceeds to us of approximately $74.0 million.

In July and August 2015, holders of $21.0 million principal amount of our 2020 Convertible Notes elected to convert the principal into 3,333,319 shares of common stock. In addition, the Interest Make-Whole Payment was settled with shares of common stock, at our election, resulting in the issuance of 530,072 additional shares of common stock. As a result of these conversions, we no longer have an obligation to repay the principal or make cash interest payments on the 2020 Convertible Notes.

In the first quarter of 2015, we completed our IPO and concurrent offering of the 2020 Convertible Notes resulting in aggregate net proceeds to us of approximately $55.4 million.

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

	For the Years Ended December 31,	
(in thousands)	**2016**	**2015**
Cash used in operating activities	$ (37,266)	$ (17,416)
Cash used in investing activities	(66,059)	(31,675)
Cash provided by financing activities	53,081	125,515
Net increase (decrease) in cash and equivalents	$ (50,244)	$ 76,424

Net cash used in operating activities

Net cash used in operating activities was $37.3 million for the year ended December 31, 2016, and principally resulted from our net loss of $42.9 million, partially offset by $2.9 million in noncash stock-based compensation and a $2.1 million net change in operating assets and liabilities.

Net cash used in operating activities was $17.4 million for the year ended December 31, 2015, and principally resulted from our net loss of $68.0 million, increases of prepaid expenses and other assets of $1.3 million and decreases in non-cash expenses related changes in fair value of warrant liabilities and Convertible Bridge Notes redemption rights derivative of $0.7 million. These amounts were partially offset by increases in non-cash expenses related to changes in the fair value of our 2020 Convertible Notes derivative liability of $42.8 million, loss on extinguishment of debt of $4.2 million, stock-based compensation of $2.4 million, increases in accounts payables and accrued expenses of $1.9 million and non-cash interest expense of $1.1 million.

Net cash used in investing activities

Net cash used in investing activities was $66.1 million for the year ended December 31, 2016, and related primarily to the purchase of $122.3 million of short-term investments and $56.7 million of proceeds from the maturity of short-term investments. Additionally, we purchased $0.5 million of property and equipment in the year ended December 31, 2016.

Net cash used in investing activities was $31.7 million for the year ended December 31, 2015, and related primarily to the purchase of $33.7 million of short-term investments, $2.4 million of proceeds from the maturity of short-term investments, and $0.4 million of purchases of property and equipment.

Net cash provided by financing activities

Net cash provided by financing activities was $53.1 million for the year ended December 31, 2016 and primarily reflects net proceeds of $48.7 million from the issuance of our 2021 Convertible Notes and net proceeds of $4.0 million from the issuance of common stock pursuant to our ATM.

Net cash provided by financing activities was $125.5 million for the year ended December 31, 2015, and reflects the net proceeds from (i) the issuance of common stock in our IPO of $38.1 million, (ii) our offering of 2020 Convertible Notes of $19.1 million, and (iii) the issuance of common stock in the Follow-on Offering of $74.0 million. These net proceeds from our common stock and 2020 Convertible Notes in 2015 do not reflect an aggregate of $1.8 million of IPO-related costs incurred in 2014. Additionally, in 2015, we made $5.8 million of payments related to the principal and termination of our notes payable.

Operating Capital Requirements

To date, we have not generated any revenue from product sales. We do not know when, or if, we will generate any revenue from product sales. We do not expect to generate significant revenue from product sales unless and until we obtain regulatory approval of and commercialize one of our current or future product candidates. We anticipate that we will continue to generate losses for the foreseeable future and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates and begin to commercialize any approved products. Since the closing of our IPO in February 2015, we are incurring additional costs associated with operating as a public company. In addition, subject to obtaining regulatory approval of any of our product candidates, we expect to incur significant commercialization expenses for product sales, marketing and manufacturing. Accordingly, we anticipate that we will need substantial additional funding in connection with our continuing operations.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. To the extent that we are able to raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could cause potential dilution. If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or research programs or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following summarizes our significant contractual obligations as of December 31, 2016:

(in thousands)	Total	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years
Operating facilities lease (1)	$ 2,622	$ 402	$ 831	$ 869	$ 520
2021 Convertible Notes (2)	66,950	2,990	5,980	57,980	-
Total	$ 69,572	$ 3,392	$ 6,811	$ 58,849	$ 520

(1) In May 2015, we entered into a lease agreement for our new headquarters in Lexington, Massachusetts. We occupied this space in September 2015 and the lease term commenced in the same month. In February 2016, we amended this lease by leasing an additional 3,888 square feet which we occupied in July 2016, and the lease term commenced in the same month.

(2) Amounts represent principal and interest on our 2021 Convertible Notes.

We enter into contracts in the normal course of business with CROs and contract manufacturers 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, they are not included in the table of contractual obligations and commitments.

Off-Balance Sheet Arrangements

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

Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations. We had cash and cash equivalents of $29.8 million at December 31, 2016, consisting primarily of funds in money market accounts. We also had $96.7 million in short-term investments consisting of certificates of deposit, agency bonds and United States Treasury securities. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 1.0% increase in interest rates would have a material effect on the fair market value of our portfolio, and accordingly we do not expect a sudden change in market interest rates to affect materially our operating results or cash flows.

JOBS Act

Under Section 107(b) of the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, an "emerging growth company" can delay the adoption of new or revised accounting standards until such time as those standards would apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, as a result, we will adopt new or revised accounting standards at the same time as other public companies that are not emerging growth companies. There are other exemptions and reduced reporting requirements provided by the JOBS Act that we are currently evaluating. For example, as an emerging growth company, we are exempt from Sections 14A(a) and (b) of the Exchange Act which would otherwise require us to (i) submit certain executive compensation matters to stockholder advisory votes, such as "say-on-pay," "say-on-frequency" and "golden parachutes" and (ii) disclose certain executive compensation related items such as the correlation between executive compensation and performance and comparisons of our Chief Executive Officer's compensation to our median employee compensation. We also intend to rely on an exemption from the rule requiring us to provide an auditor's attestation report on our internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act and the rule requiring us to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board, or PCAOB, regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the consolidated financial statements as the auditor discussion and analysis. We will continue to remain an "emerging growth company" until the earliest of the following: December 31, 2020; the last day of the fiscal year in which our total annual gross revenue is equal to or more than $1 billion; the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

Critical Accounting Policies and Estimates

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with performing research and development services on our behalf;
- investigative sites or other providers in connection with clinical trials;
- vendors in connection with non-clinical development activities; and
- vendors related to product manufacturing, development and distribution of clinical supplies.

We base our expenses related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage non-clinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed, enrollment of patients, number of sites activated and level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting expenses that are too high or too low in any particular period.

Fair Value Measurements

We are required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. Accounting Standard Codification, or ASC, Topic 820, Fair Value Measurements and Disclosures, establishes a hierarchy of inputs used when available. Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of our company. Unobservable inputs are inputs that reflect our assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The three levels of the fair value hierarchy are described below:

- Level 1—Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that we have the ability to access at the measurement date;
- Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly;
- Level 3—Valuations that require inputs that reflect our own assumptions that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by us in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Our material financial instruments at December 31, 2016 and 2015, consisted of cash and cash equivalents and short-term investments. We have determined that our United States Treasury securities are subject to Level 1 fair value measurements as these assets are valued using quoted market prices in active markets without any valuation adjustments. We have determined that our certificates of deposit are categorized as Level 2 assets under the fair value hierarchy, as there are no quoted market prices in active markets, and our agency bonds as Level 2 assets under the fair value hierarchy, as these assets are not always valued daily using quoted market prices in active markets.

Stock-Based Compensation

We measure the cost of employee services received in exchange for an award of equity instruments based on the grant date fair value of the award. That cost is recognized on a straight-line basis over the period during which the employee is required to provide service in exchange for the award. The fair value of options on the date of grant is calculated using the Black-Scholes option pricing model based on key assumptions such as stock price, expected volatility and expected term. The fair value of restricted stock awards is based on the intrinsic value of such awards on the date of grant. Compensation cost for stock purchase rights under our employee stock purchase plan is measured and recognized on the date that we become obligated to issue shares of our common stock and is based on the difference between the fair value of our common stock and the purchase price on such date. Our estimates of these assumptions are primarily based on third-party valuations, historical data, peer company data and judgment regarding future trends and factors.

We account for stock options issued to non-employees in accordance with the provisions of the Financial Accounting Standards Board, or FASB, ASC Subtopic 505-50, *Equity-Based Payments to Non-employees*, which requires valuing the stock options using the Black-Scholes option pricing model and re-measuring such stock options at their current fair value as they vest.

Significant Factors, Assumptions and Methodologies Used in Determining Fair Value

Determining the fair value of our convertible preferred stock warrants, convertible debt derivative and stock-based awards requires the use of subjective assumptions. In the absence of a publicly traded market for our securities, we conducted periodic valuations of our securities.

Valuations conducted in 2015 and 2014

A third-party valuation consultant was engaged to advise and assist us in connection with the valuations of our (i) Series AA preferred stock warrants outstanding at December 31, 2014, (ii) our convertible debt redemption rights derivative at issuance and at December 31, 2014, (iii) our common stock options issued in August 2014 and (iv) our 2020 Convertible Notes derivative liability at issuance and at the time of the conversions of the 2020 Convertible Notes during 2015. Because our previously outstanding Series X preferred stock was entitled to a contingent liquidation preference which varies based on the total value of our equity, we were precluded from using a closed-form model, such as the Black-Scholes option pricing method, to value the Series AA preferred stock warrants. Therefore, we employed a Monte Carlo simulation methodology to determine the fair value of securities in our capital structure during the period during the period prior to the February 2015 IPO.

Common Stock and Preferred Stock Warrant Valuations

Our initial equity value was determined by utilizing a risk-adjusted discounted cash flow model based upon market research and management's assessment thereof, which is an income approach and was corroborated with market data, coupled with a series of Monte Carlo simulations which projected various equity values under different possible liquidity events including (i) initial public offering ("IPO"), (ii) merger and acquisition ("M&A"), and (iii) stay-private ("SP") scenarios. The first two scenarios assumed positive results from our recent Phase 2 clinical trial, while the third scenario considered unfavorable results for valuations performed prior to December 31, 2014 and, at December 31, 2014, no IPO or M&A transaction.

Key assumptions underlying the discounted cash flow model are described below:

- Based on the research and industry knowledge of our officers and consultants, we developed projections of market penetration, product selling prices and required infrastructure to estimate our future revenues and operating expenses to determine projected free cash flows from our two current product candidates containing *trabodenoson*, through patent expiration.
- *Probability of Success*. To determine the probability of success for the various phases of development required for submission in an NDA, we utilized the clinical trial success rates as published in certain reports.
- *Time to Liquidity*. All 2014 valuations assumed liquidity events occurring between December 31, 2014 and April 1, 2015.
- *Risk Free rates*. Risk free rates are based on published or imputed government treasury rates as of each valuation date.
- *Volatilities*. Volatilities were derived from historical data from guideline publicly traded comparable companies. We used volatilities of 60% to 70% for the 2014 valuations.

The Monte Carlo-simulated total equity values were then allocated to each type of security using a current value (waterfall) method under each scenario and were then probability-adjusted using probability weights by scenario.

As of date:	IPO	M&A	SP
December 31, 2014	70%	25%	5%

Valuation models require the input of highly subjective assumptions. Because our shares had characteristics significantly different from that of publicly traded common stock and because changes in the subjective input assumptions can materially affect the fair value estimate, in management's opinion, the existing models did not necessarily provide a reliable, single measure of the fair value of our previously outstanding Series AA preferred stock or Series X preferred stock. The foregoing valuation methodologies were not the only valuation methodologies available and will not be expected to be used to value our securities after our IPO. We cannot make complete assurances as to any particular valuation for our securities.

Convertible Debt Redemption Rights Derivative

The Convertible Bridge Notes redemption rights derivative required separate accounting and was valued using a single income valuation approach. We estimated the fair value of the redemption rights derivative using a ''with and without'' income valuation approach. Under this approach, we estimated the present value of the fixed interest rate debt based on the fair value of similar debt instruments excluding the embedded feature. This amount was then compared to the fair value of the debt instrument including the embedded feature using a probability weighted approach by assigning each embedded derivative feature a probability of occurrence, with consideration provided for the settlement amount including conversion discounts, prepayment penalties, the expected life of the liability and the applicable discount rate.

As of the issuance of the Convertible Bridge Notes on December 22, 2014 and on December 31, 2014, the Company ascribed a probability of occurrence of 25% to the change in control redemption feature of the Convertible Bridge Notes. The expected life of the feature was the remaining term of the debt and the discount rate was 18.9%. The Company classified the liability within Level 3 of the fair value hierarchy as the probability factor and the discount rate are unobservable inputs and significant to the valuation model.

2020 Convertible Notes derivative liability

Based on the characteristics of the (i) conversion option including make-whole provision, (ii) the Additional Interest, and (iii) the notes, we estimated the fair value of the conversion option including make-whole and the Additional Interest using the "with" and "without" method. Using this methodology, we first valued the notes with the conversion option including make-whole provision but excluding the Additional Interest (the "with" scenario) and subsequently valued the notes without the conversion option including make-whole provision and excluding the Additional Interest (the "without" scenario). The difference between the fair values of the notes in the "with" and "without" scenarios was the concluded fair value of the conversion option including make-whole provision as

of the measurement date. We developed an estimate of fair value for the notes excluding the Additional Interest using a binomial lattice model. We modeled the decision to convert or hold by considering the maximum of the conversion or hold value at every node of the lattice in which the notes are convertible and choosing the action that maximizes the return to the notes' holders. The significant assumptions used in the binomial model were: the market yield and the expected volatility.

We estimated the fair value of the Additional Interest using an income approach, specifically, the risk-neutral debt valuation method that is used to derive the value of a debt instrument using the expected cash flows and the risk-free rate. The significant assumptions used in estimating the expected cash flows were the market yield used to determine the risk-neutral probability of default and the expected recovery rate upon default.

Recent Accounting Pronouncements

In August 2014, the FASB issued Accounting Standards Update ("ASU") 2014-15, *Presentation of Financial Statements – Going Concern*, which provides guidance about management's responsibility to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. The new standard is effective for the annual period ending after December 15, 2016 and for annual and interim periods thereafter, with early adoption permitted. We adopted this standard for the year ended December 31, 2016. The adoption of this ASU does not have a material impact on our consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases* (Topic 842), which supersedes the current leasing guidance and upon adoption, will require lessees to recognize right-of-use assets and lease liabilities on the balance sheet for all leases with terms longer than 12 months. The new standard is effective for the annual period beginning after December 15, 2018, and can be early adopted by applying a modified retrospective approach for leases existing at, and entered into after, the beginning of the earliest comparable period presented in the financial statements. We are currently evaluating the impact of this accounting standard update on our consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, which amends ASC Topic 718, *Compensation – Stock Compensation*, and includes provisions intended to simplify various aspects related to how share-based payments are accounted for and presented in the financial statements. The new standard is effective for the annual period beginning after December 15, 2016, and for annual and interim periods thereafter, with early adoption permitted. The adoption of this guidance is not expected to have a material impact on our consolidated financial statements.

Item 7A. Quantitative and Qualitative Disclosures about Market Risks

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations. We had cash and cash equivalents of $29.8 million at December 31, 2016, consisting primarily of funds in money market accounts. We also had $96.7 million in short-term investments consisting of certificates of deposit, agency bonds and United States Treasury securities. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 1.0% increase in interest rates would have a material effect on the fair market value of our portfolio, and accordingly we do not expect a sudden change in market interest rates to affect materially our operating results or cash flows.

Our 2021 Convertible Notes bear interest at a fixed rate and therefore a change in interest rates would not impact the amount of interest we would have paid on this indebtedness. Until the 2020 Convertible Notes were converted in July and August 2015, they bore interest at a fixed rate, therefore a change in interest rates would not impact the amount of interest we would have paid on this indebtedness.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15.

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 principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of December 31, 2016, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act are 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 us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial and accounting officer, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial and accounting officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States ("GAAP"). Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2016. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its 2013 *Internal Control — Integrated Framework*. Based on this assessment, our management has concluded that, as of December 31, 2016, our internal control over financial reporting is effective based on those criteria.

This annual report on Form 10-K does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting. Management's report was not subject to attestation by our independent registered public accounting firm pursuant to an exemption under Section 989G of the Dodd-Frank Wall Street Reform and Consumer Protection Act made available to us under the Jumpstart Our Business Startups Act of 2012.

Inherent Limitations of Internal Controls

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. 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.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the period covered by this report that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Not applicable.

PART III. — OTHER INFORMATION

Item 10. Directors, Executive Officers and Corporate Governance

Directors and Executive Officers

The following table sets forth information regarding our executive officers and directors, including their respective ages and positions as of the date hereof:

Name	Age	Position
Executive Officers:		
David P. Southwell	56	President, Chief Executive Officer and Director
Rudolf Baumgartner, M.D.	57	Executive Vice President and Chief Medical Officer
William K. McVicar, Ph.D. (1)	59	Former Executive Vice President and Chief Scientific Officer
Dale Ritter	66	Vice President—Finance
Non-Management Directors:		
Timothy Barberich (3)	69	Director
Carsten Boess (2)(4)	50	Director
J. Martin Carroll	67	Director
Paul G. Howes (2)	62	Director
Patrick Machado (2)	53	Director
Gary Phillips, M.D. (3)	50	Director
Richard N. Spivey, PharmD, PhD (3)(4)	67	Director

(1) Dr. McVicar served as Executive Vice President and Chief Scientific Officer until October 4, 2016
(2) Member of the Audit Committee.
(3) Member of the Compensation Committee.
(4) Member of the Nominating and Corporate Governance Committee.

The following is a biographical summary of the experience of our executive officers and directors:

Executive Officers

David P. Southwell has served as our President and Chief Executive Officer since July 2014, and as one of our directors since August 2014. From March 2010 to October 2012, Mr. Southwell served as Executive Vice President, Chief Financial Officer of Human Genome Sciences, Inc., or Human Genome Sciences, which is owned by GlaxoSmithKline plc. Prior to his time at Human Genome Sciences, Mr. Southwell served as Executive Vice President and Chief Financial Officer of Sepracor Inc. from July 1994 to July 2008. Mr. Southwell has also served on the Board of Directors of PTC Therapeutics Inc. since December 2005 and THL Credit, Inc. since June 2007. Mr. Southwell received a B.A. from Rice University and an M.B.A. from Dartmouth College. We believe that Mr. Southwell's qualifications to sit on our Board include his broad experience serving on the boards of directors of public companies, his specific experience with public therapeutics companies and his executive leadership, managerial and business experience.

Rudolf Baumgartner, M.D. has served as our Executive Vice President and Chief Medical Officer since June 2007. Dr. Baumgartner received a B.S. and an M.D. from Pennsylvania State University and completed post-doctoral training at the University of Michigan, Johns Hopkins University and the National Institutes of Health.

William K. McVicar, Ph.D. joined us in September 2007 as Executive Vice President, Pharmaceutical Development and served as our Executive Vice President and Chief Scientific Officer from January 2009 to October 2016. Dr. McVicar also served as our interim President from May 2013 until August 2014. Dr. McVicar now serves as a Senior Advisor to the Company until April 4, 2017. Dr. McVicar received a B.S. from the State University of New York College at Oneonta and a Ph.D. in Chemistry from the University of Vermont.

Dale Ritter joined us as a financial consultant in June 2014 and has served as our Vice President—Finance and Principal Financial and Accounting Officer, Treasurer and Secretary since August 2014. From May 2011 to November 2013, Mr. Ritter served Senior Vice President, Finance and Chief Accounting Officer at Coronado Biosciences, Inc. From January 2011 to May 2011, Mr. Ritter served as an Independent Financial Consultant and from 1994 to 2009 Mr. Ritter served in various roles and most recently as Senior Vice President and Chief Accounting Officer at Indevus Pharmaceuticals, Inc. Mr. Ritter received a B.A. from Syracuse University and an M.B.A. from Babson College.

Non-Management Directors

Timothy Barberich has served as one of our directors since September 2016. Mr. Barberich served as Chief Executive Officer of Sepracor Inc. from 1984 to 2007 and as Chairman of its Board from 1994 to 2009. Prior to working for Sepracor Inc., Mr. Barberich held positions at Millipore Corporation and American Cyanamid Company. Mr. Barberich has served as a member of the Board of Directors at GI Dynamics, Inc. since 2011, Verastem, Inc. since 2014, Neurovance, Inc. since 2010, Frequency Therapeutics, Inc. since 2016 and BioNevia LLC since 2008. Mr. Barberich also served on the Board of Directors of Heartware, Inc. from 2008 to 2016, Tokai Pharmaceuticals, Inc. from 2009 to 2016 and MirImmune, Inc. from 2015 to 2017. Mr. Barberich received his Bachelor of Science degree in Chemistry from King's College. We believe that Mr. Barberich's qualifications to sit on our Board include his experience as a director of and working in leadership roles at pharmaceutical companies.

Carsten Boess has served as one of our directors since January 2016. He is currently the Chief Business Officer at Kiniksa Pharmaceuticals, a privately held biotechnology company. He previously served as Senior Vice President and Chief Financial Officer at Synageva Biopharma Corporation from 2011 until the company's acquisition by Alexion Pharmaceuticals in 2015. Prior to his role at Synageva, Mr. Boess served in multiple roles with increasing responsibility for Insulet Corporation, including Chief Financial Officer from 2006 to 2009 and Vice President of International Operations from 2009 to 2011. Prior to that, Mr. Boess served as Executive Vice President of Finance for Serono Inc. from 2005 to 2006. In addition, he was a member of the Geneva based World Wide Executive Finance Management Team while at Serono. Mr. Boess was also Chief Financial Officer at Alexion Pharmaceuticals, and was a finance executive at Novozymes of North America and Novo Nordisk in France, Switzerland and China. Mr. Boess received a Bachelor's degree and Master's degree in Economics and Finance, specializing in Accounting and Finance from the University of Odense, Denmark. We believe that Mr. Boess' qualifications to sit on our Board include his business and financial experience working at pharmaceutical companies.

J. Martin Carroll has served as one of our directors since April 2016. In 2012, Mr. Carroll held a position leading corporate strategy and development for Boehringer Ingelheim GmBH in Ingelheim, Germany. From 2002 to 2011, he was President and CEO of US Businesses for Boehringer Ingelheim Corporation. From 1976 to 2001, Mr. Carroll held various positions at Merck & Company, Inc., including Executive Vice President – Customer Marketing and Sales. From 1972 to 1976, Mr. Carroll served in the United States Air Force. Mr. Carroll has served as a member of the Board of Directors at Catalent, Inc. and TherapeuticsMD, Inc. since 2015, and Mallinckrodt Pharmaceuticals since 2013. He has previously served on the Boards of Accredo Health Group, Inc. and Durata Therapeutics, Inc. Mr. Carroll received his Bachelor degree from College of the Holy Cross and his MBA from Babson College. We believe that Mr. Carroll's qualifications to serve on our Board include his significant experience in leadership positions at pharmaceutical companies.

Paul G. Howes has served as one of our directors since September 2008. From January 2016 to present, Mr. Howes has been President of ThromboGenics Inc. Mr. Howes also served as our President and Chief Executive Officer from September 2008 to May 2013. Prior to his time with us, Mr. Howes served as President of the Americas Region of Bausch + Lomb Incorporated, which is now owned by Valeant Pharmaceuticals International, Inc., from July 2003 to February 2007. Prior to this time, Mr. Howes served in a variety of senior roles at Merck & Co., Inc. for sixteen years. Since May 2013, Mr. Howes has served as a member of the Board of Directors of various companies including: since May 2013, Kish Bancorp and Kish Bank, a financial conglomerate parent company and its community bank subsidiary; since November 2008, Prevent Blindness America, a vision-related charity for which Mr. Howes has served as Chairman since November 2013; since August 2014, ThromboGenics NV and ThromboGenics Inc., a global integrated biopharmaceutical company and its U.S.-based operating subsidiary. Mr. Howes received an A.B. from Harvard University and an M.B.A. from York University. We believe that Mr. Howes' qualifications to sit on our Board include the intimate knowledge of our operations he developed as our President and Chief Executive Officer, his experience working with a public biopharmaceutical company, significant commercial experience in the field of ophthalmology and his executive leadership, managerial and business experience.

Patrick Machado has served as one of our directors since August 2016. Mr. Machado co-founded Medivation, Inc. and served as its Chief Business Officer from December 2009 to April 2014 and its Chief Financial Officer from December 2004 to April 2014. Prior to working for Medivation, Inc., Mr. Machado held positions at Cytyc Corporation, Pro•Duct Health, Inc., Chiron Corporation and Morrison & Foerster LLP. Mr. Machado has served as a member of the Board of Directors at Chimerix, Inc. since 2014, as a member of the Board of Directors of Scynexis, Inc. since 2015, and as a member of the Board of Directors of Medivation, Inc. from 2014 to 2016. Mr. Machado received his Bachelor of Science in Economics and Bachelor of Arts in German from Santa Clara University and his Juris Doctor from Harvard Law School. We believe that Mr. Machado's qualifications to sit on our Board include his experience working as a director of and in leadership roles at pharmaceutical companies.

Gary Phillips, M.D. has served as one of our directors since October 2015. Dr. Phillips has also served on the Board of Directors of Aldeyra Therapeutics since 2009. From October 2013 and to the present, Dr. Phillips has been Senior Vice President, Chief Strategy Officer at Mallinckrodt Pharmaceuticals plc. He was also Senior Vice President and President of Autoimmune and Rare Diseases at Mallinckrodt from August to January 2015. Dr. Phillips was Head of Global Health & Healthcare Industries at the

World Economic Forum in Geneva from January 2012 to September 2013. He was President of Reckitt Benckiser Pharmaceuticals, Inc. (now Indivior) from 2011 to 2012. He served as President of U.S. Surgical and Pharmaceuticals at Bausch & Lomb from 2002 to 2008. Dr. Phillips has also held executive roles at Merck Serono SA (a division of Merck KGaA) from 2008 to 2011, Novartis Corporation from 2000 to 2002, and Wyeth Pharmaceuticals, Inc. (now Pfizer, Inc.) from 1999 to 2000. Dr. Phillips was a healthcare strategy managing consultant at Towers Perrin (now Towers Watson & Co) from 1997 to 1999, and practiced as a general medicine clinician/officer in the US Navy, from which he was honorably discharged as a lieutenant commander. Dr. Phillips was educated at the University of Pennsylvania, where he received an M.D. (Alpha Omega Alpha) from the School of Medicine, an MBA from the Wharton School, and B.A. (summa cum laude, Phi Beta Kappa) in biochemistry with distinction from the School of Arts and Sciences. He completed postgraduate medical education at United States Naval Medical Center and maintains an active medical license. Currently, he serves on the boards of Aldeyra Therapeutics (NASDAQ: ALDX), Envisia Therapeutics, and Rheon Medical SA. We believe that Dr. Phillips' qualifications to sit on our Board include his experience working in leadership roles at pharmaceutical companies.

Richard N. Spivey, PharmD, PhD has served as one of our directors since July 2015. Dr. Spivey currently serves as a scientific advisor to the pharmaceutical industry and as a member of the Board of Councilors, University of Southern California, and School of Pharmacy. From 2010 to 2015, he was the Senior Vice President, Global Regulatory Affairs at Allergan, plc. From 2002 to 2010, Dr. Spivey served various roles at Meda AB (previously MedPointe Inc.), most recently as the Chief Scientific Officer (Head of R&D). Dr. Spivey has also held positions at Pharmacia Corporation (now Pfizer Inc.), Schering-Plough Corporation (now Merck & Co.), Parke-Davis Pharmaceutical Research Division, and Boots Pharmaceuticals, Inc. Dr. Spivey received his PharmD from the University of Southern California and his PhD from the College of Pharmacy, University of Minnesota. We believe that Dr. Spivey's qualifications to sit on our Board include his distinguished background in drug development and regulatory affairs spanning thirty-years of experience working at leading pharmaceutical companies.

Composition of Our Board of Directors

Our Board of Directors currently consists of eight members. Our nominating and governance committee and Board of Directors may consider a broad range of factors relating to the qualifications and background of nominees, which may include diversity and is not limited to race, gender or national origin. We have no formal policy regarding board diversity. Our nominating and governance committee's and Board of Directors' priority in selecting board members is identification of persons who will further the interests of our stockholders through his or her established record of professional accomplishment, the ability to contribute positively to the collaborative culture among board members, knowledge of our business, understanding of the competitive landscape and professional and personal experiences and expertise relevant to our growth strategy. Our directors hold office until their successors have been elected and qualified or until the earlier of their resignation or removal.

Our amended and restated certificate of incorporation and amended and restated bylaws also provide that our directors may be removed only for cause by the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in an annual election of directors, and that any vacancy on our Board of Directors, including a vacancy resulting from an enlargement of our Board of Directors, may be filled only by vote of a majority of our directors then in office.

Director independence. Our Board of Directors has determined that all members of the Board of Directors except Mr. Southwell, are independent, as determined in accordance with the rules of The NASDAQ Global Market, or NASDAQ. Our Board of Directors also determined that our former directors, Dr. A.N. "Jerry" Karabelas, Mr. Isai Peimer, Mr. Ittai Harel and Mr. Martin Vogelbaum, satisfied the independence requirements, as determined in accordance with the rules of NASDAQ. In making such independence determination, the Board of Directors considered the relationships that each such non-employee director has with us and all other facts and circumstances that the Board of Directors deemed relevant in determining their independence, including the beneficial ownership of our capital stock by each non-employee director. In considering the independence of the directors listed above, our Board of Directors considered the association of our directors with the holders of more than 5% of our common stock. The composition and functioning of our Board of Directors and each of our committees complies with all applicable requirements of NASDAQ and the rules and regulations of the SEC. There are no family relationships among any of our directors or executive officers.

Staggered board. In accordance with the terms of our amended and restated certificate of incorporation and amended and restated bylaws, our Board of Directors is divided into three classes, Class I, Class II and Class III, with each class serving staggered three-year terms. Upon the expiration of the term of a class of directors, directors in that class will be eligible to be elected for a new three-year term at the annual meeting of stockholders in the year in which their term expires. The following persons have been designated to serve as directors in the following classes until the term specified below or until his earlier death, resignation or removal:

- Our Class I directors are David P. Southwell and Richard N. Spivey, PharmD, PhD (term expires on date of annual meeting of stockholders following the year ending December 31, 2017);

- Our Class II directors are J. Martin Carroll, Gary M. Phillips, and Carsten Boess (term expires on date of annual meeting of stockholders following the year ending December 31, 2018); and
- Our Class III directors are Paul G. Howes, Patrick Machado and Timothy Barberich (term expires on date of annual meeting of stockholders following the year ending December 31, 2016).

Our amended and restated certificate of incorporation and amended and restated bylaws provide that the authorized number of directors may be changed only by resolution of the Board of Directors. Any additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class shall consist of one third of the Board of Directors.

The division of our Board of Directors into three classes with staggered three-year terms may delay or prevent stockholder efforts to effect a change of our management or a change in control.

Board Leadership Structure and Board's Role in Risk Oversight

The positions of our Chairperson of the board and Chief Executive Officer are presently separated. Separating these positions allows our Chief Executive Officer to focus on our day-to-day business, while allowing the Chairperson of the board to lead the Board of Directors in its fundamental role of providing advice to and independent oversight of management. Our Board of Directors recognizes the time, effort and energy that the Chief Executive Officer must devote to his position in the current business environment, as well as the commitment required to serve as our Chairperson, particularly as the Board of Directors' oversight responsibilities continue to grow. Our Board of Directors also believes that this structure ensures a greater role for the independent directors in the oversight of our company and active participation of the independent directors in setting agendas and establishing priorities and procedures for the work of our Board of Directors. Our Board of Directors believes its administration of its risk oversight function has not affected its leadership structure. Although our amended and restated bylaws do not require our Chairperson and Chief Executive Officer positions to be separate, our Board of Directors believes that having separate positions is the appropriate leadership structure for us at this time and demonstrates our commitment to good corporate governance.

Our Board of Directors oversees the management of risks inherent in the operation of our business and the implementation of our business strategies. Our Board of Directors performs this oversight role by using several different levels of review. In connection with its reviews of our operations and corporate functions, our Board of Directors addresses the primary risks associated with those operations and corporate functions. In addition, our Board of Directors reviews the risks associated with our business strategies periodically throughout the year as part of its consideration of undertaking any such business strategies.

Director Nomination Process

There have been no material changes to the process by which stockholders may submit nominees for election to the Board of Directors to the Nominating and Corporate Governance Committee since that process was described in the Company's Proxy Statement filed with the SEC on May 6, 2016.

Board Committees

Our Board of Directors has established an audit committee, a compensation committee and a nominating and corporate governance committee, each of which operates pursuant to a separate charter adopted by our Board of Directors. The composition and functioning of all of our committees will comply with all applicable requirements of the Sarbanes-Oxley Act, the Dodd-Frank Act, NASDAQ and SEC rules and regulations.

Audit Committee

Carsten Boess, Paul G. Howes and Patrick Machado currently serve on the audit committee, which is chaired by Carsten Boess. Our Board of Directors has determined that each member of the audit committee is "independent" for audit committee purposes as that term is defined in the rules of the SEC and the applicable rules of NASDAQ. Our Board of Directors has designated Carsten Boess as an "audit committee financial expert," as defined under the applicable rules of the SEC. The audit committee's responsibilities include:

- appointing, approving the compensation of, and assessing the independence of our independent registered public accounting firm;
- approving auditing and permissible non-audit services, and the terms of such services, to be provided by our independent registered public accounting firm;

- reviewing the internal audit plan with the independent registered public accounting firm and members of management responsible for preparing our financial statements;
- reviewing and discussing with management and the independent registered public accounting firm our annual and quarterly financial statements and related disclosures as well as critical accounting policies and practices used by us;
- reviewing the adequacy of our internal control over financial reporting;
- establishing policies and procedures for the receipt, retention and treatment of complaints received regarding ethics-related issues or potential violations of our code of business conduct and ethics and accounting and auditing-related complaints and concerns;
- recommending, based upon the audit committee's review and discussions with management and the independent registered public accounting firm, whether our audited financial statements shall be included in our Annual Report on Form 10-K;
- monitoring the integrity of our financial statements and our compliance with legal and regulatory requirements as they relate to our financial statements and accounting matters;
- preparing the audit committee report required by SEC rules to be included in our annual proxy statement;
- reviewing all related party transactions for potential conflict of interest situations and approving all such transactions; and
- reviewing quarterly earnings releases.

Compensation Committee

Timothy Barberich, Gary Phillips, M.D., and Richard N. Spivey, PharmD, PhD currently serve on the compensation committee, which is chaired by Timothy Barberich. Our Board of Directors has determined that each member of the compensation committee is "independent" as that term is defined in the applicable rules of NASDAQ. The compensation committee's responsibilities include:

- annually reviewing and approving corporate goals and objectives relevant to the compensation of our Chief Executive Officer;
- evaluating the performance of our Chief Executive Officer in light of such corporate goals and objectives and determining the compensation of our Chief Executive Officer;
- reviewing and approving the compensation of our other executive officers;
- reviewing and establishing our overall management compensation, philosophy and policy;
- overseeing and administering our compensation and similar plans;
- evaluating and assessing potential current compensation advisors in accordance with the independence standards identified in the applicable rules of NASDAQ;
- retaining and approving the compensation of any compensation advisors;
- reviewing and approving our policies and procedures for the grant of equity-based awards;
- reviewing and making recommendations to the Board of Directors with respect to director compensation;
- preparing the compensation committee report required by SEC rules to be included in our annual proxy statement;
- reviewing and discussing with management the compensation discussion and analysis to be included in our annual proxy statement or Annual Report on Form 10-K; and
- reviewing and discussing with the Board of Directors corporate succession plans for the Chief Executive Officer and other key officers.

Nominating and Corporate Governance Committee

Carsten Boess and Richard N. Spivey, PharmD, PhD currently serve on the nominating and corporate governance committee, which is chaired by Richard N. Spivey, PharmD, PhD. Our Board of Directors has determined that each member of the nominating and corporate governance committee is "independent" as that term is defined in the applicable rules of NASDAQ. The nominating and corporate governance committee's responsibilities include:

- developing and recommending to the Board of Directors criteria for board and committee membership;

- establishing procedures for identifying and evaluating board of director candidates, including nominees recommended by stockholders;
- identifying individuals qualified to become members of the Board of Directors;
- recommending to the Board of Directors the persons to be nominated for election as directors and to each of the board's committees;
- developing and recommending to the Board of Directors a set of corporate governance guidelines; and
- overseeing the evaluation of the Board of Directors and management.

Corporate Governance

Our Board of Directors has adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions. A current copy of the code is posted on the Corporate Governance section of our website, which is located at www.inotekpharma.com. If we make any substantive amendments to, or grant any waivers from, the code of business conduct and ethics for any officer, we will disclose the nature of such amendment or waiver on our website or in a current report on Form 8-K.

Item 11. Executive Compensation

The following table sets forth the portion of compensation paid to the named executive officers that is attributable to services performed during the fiscal year ended December 31, 2016 and 2015.

Name and principal position	Fiscal Year	Salary $	Bonus $		Option Awards $ (3)	Stock Awards $ (4)	All other compensation $ (5)	Total $
David P. Southwell	2016	465,508	221,231	(1)	1,093,470	2,275,000	5,273	4,060,482
President and Chief Executive Officer	2015	440,152	257,000	(2)	602,912	—	138	1,300,202
Rudolf Baumgartner, M.D.	2016	393,095	144,538	(1)	839,175	780,000	9,761	2,166,569
Executive Vice President and Chief Medical Officer	2015	387,124	152,000	(2)	301,456	—	8,208	848,788
William K. McVicar, Ph.D.	2016	382,750	101,806	(1)	686,598	—	9,761	1,180,915
Former Executive Vice President and Chief Scientific Officer (6)	2015	372,523	148,000	(2)	301,456	—	8,208	830,187
Dale Ritter	2016	274,093	86,384	(1)	203,436	—	11,367	575,280
Vice President—Finance	2015	273,385	107,000	(2)	100,485	—	6,779	487,649

(1) For Mr. Southwell, Dr. Baumgartner and Mr. Ritter, represents bonus amounts earned in 2016 and paid in 2017. For Dr. McVicar, represents the amount of bonus paid in 2017 pursuant to his Transition Agreement.

(2) Represents bonus amounts earned in 2015 and paid in 2016.

(3) Reflects the grant date fair value of option awards, calculated in accordance with ASC Topic 718, disregarding the estimate on forfeitures. The assumptions we used for calculating grant date fair values are set forth in Note 8 of Notes to Consolidated Financial Statements in this Form 10-K.

(4) Reflects the grant date fair value of stock awards, calculated in accordance with ASC Topic 718. The assumptions we used for calculating grant date fair values are set forth in Note 8 of Notes to Consolidated Financial Statements in this Form 10-K.

(5) For 2016 consists of: for Mr. Southwell, $3,462 of matching contributions pursuant to the Company's 401(k) Plan, $774 cost of the benefits of company-provided group-term life insurance in excess of $50,000 and $1,037 for the cost of disability insurance; for Dr. Baumgartner, $7,950 of matching contributions pursuant to the Company's 401(k) Plan, $774 for the cost of the benefits of company-provided group-term life insurance in excess of $50,000 and $1,037 for the cost of disability insurance; for Dr. McVicar, $7,950 of matching contributions pursuant to the Company's 401(k) Plan, $774 for the cost of the benefits of company-provided group-term life insurance in excess of $50,000 and $1,037 for the cost of disability insurance; for Mr. Ritter, $8,856 of matching contributions pursuant to the Company's 401(k) Plan, $1,542 for the cost of the benefits of company-provided group-term life insurance in excess of $50,000 and $969 for the cost of disability insurance. For 2015 consists of: for Mr. Southwell, cost of the benefits of company-provided group-term life insurance in excess of $50,000; for Dr. Baumgartner, $7,950 of matching contributions pursuant to the Company's 401(k) Plan and $258 for the cost of the benefits of company-provided group-term life insurance in excess of $50,000; for Dr. McVicar, $7,950 of matching contributions pursuant to the Company's 401(k) Plan and $258 for the cost of the benefits of company-provided group-term life insurance in excess of $50,000; for Mr. Ritter, $6,383 of matching contributions pursuant to the Company's 401(k) Plan and $396 for the cost of the benefits of company-provided group-term life insurance in excess of $50,000.

(6) Dr. McVicar ceased being an executive officer on October 4, 2016.

Executive Agreements

We have entered into employment agreements with certain of our named executive officers. These employment agreements provide for "at will" employment and contain the additional terms summarized below:

David P. Southwell. On August 11, 2014, we entered into an employment agreement with Mr. Southwell, our President and Chief Executive Officer. In 2016, Mr. Southwell received a base salary of $465,750, which is subject to review and adjustment in accordance with our corporate policy. In 2016, Mr. Southwell was eligible for an annual performance bonus with a target amount of 50% of his base salary. In 2016, the Compensation Committee awarded Mr. Southwell a bonus of $221,231, representing 47.5% of his 2016 base salary. Mr. Southwell is eligible to participate in our employee benefit plans in effect from time to time, subject to the terms of those plans. Subject to the execution and effectiveness of a separation agreement, including, among other things, a general release of claims, Mr. Southwell will be eligible to receive the following payments and benefits in the event that his employment is terminated by us without cause or he terminates his employment with us for good reason: base salary continuation for 12 months; if Mr. Southwell is participating in our group health plan immediately prior to the date of termination and elects COBRA health continuation, we will pay him a monthly cash payment equal to the monthly employer contribution we would have made to provide

him health insurance if he had remained employed by us until twelve months following the date of termination; and the portion of the stock options and other time-based equity awards held by Mr. Southwell as of the date of termination that would have vested in the 12 months following termination of his employment had he remained employed by us through such date shall immediately accelerate and become fully vested as of the date of termination.

Rudolf Baumgartner, M.D. On May 2, 2007, we entered into an employment agreement with Dr. Baumgartner, our Executive Vice President and Chief Medical Officer, which we amended on December 23, 2008 and October 9, 2009. In 2016, Dr. Baumgartner received a base salary of $393,300, which is subject to review and adjustment in accordance with our corporate policy. In 2016, Dr. Baumgartner was eligible for an annual performance bonus with a target amount of 35% of his base salary. In 2016, the Compensation Committee awarded Dr. Baumgartner a bonus of $144,538, representing 36.75% of his 2016 base salary. Dr. Baumgartner is eligible to participate in our employee benefit plans in effect from time to time, subject to the terms of those plans. Subject to the execution and effectiveness of a separation agreement, including, among other things, a general release of claims, Dr. Baumgartner will be eligible to receive the following payments and benefits in the event that his employment is terminated by us without cause: base salary continuation for twelve months; and a monthly cash payment equal to the monthly employer contribution to provide him health and dental insurance coverage if he had remained employed by us until 12 months following the date of termination. The receipt of the severance payments and benefits set forth above shall be conditioned upon Dr. Baumgartner not violating the terms of a restrictive covenant agreement between Dr. Baumgartner and Inotek.

William K. McVicar, Ph.D. On August 23, 2007, we entered into an employment agreement with Dr. McVicar, our Executive Vice President and Chief Scientific Officer, which we amended on December 23, 2008 and October 9, 2009. Dr. McVicar stepped down from his position as our Executive Vice President, Chief Scientific Officer and executive officer effective as of October 4, 2016. Prior to his resignation, Dr. McVicar received a base salary of $382,950, which was subject to review and adjustment in accordance with our corporate policy. In 2016, Dr. McVicar was eligible for an annual performance bonus with a target amount of 35% of his base salary, payable at the discretion of our Board. In 2016, the Compensation Committee awarded Dr. McVicar a bonus of $101,806, pursuant to the Transition Agreement. Dr. McVicar was eligible to participate in our employee benefit plans in effect from time to time, subject to the terms of those plans. Pursuant to the Transition Agreement, Dr. McVicar will be a Senior Advisor to the Company until April 4, 2017 (the "Separation Date"), and for twelve months thereafter, will continue to receive his base salary. The receipt of the severance payments and benefits set forth above shall be conditioned upon Dr. McVicar not violating the terms of a restrictive covenant agreement between Dr. McVicar and Inotek.

Dale Ritter. On August 28, 2014, we entered into an employment agreement with Mr. Ritter, our Vice President—Finance. In 2016, Mr. Ritter received an annual base salary of $274,235. Mr. Ritter is eligible for an annual performance bonus with a target amount of 30% of his annualized base salary. In 2016, the Compensation Committee awarded Mr. Ritter a bonus of $86,384, representing 31.5% of his 2016 base salary. Mr. Ritter is eligible to participate in our employee benefit plans in effect from time to time, subject to the terms of those plans. Subject to the execution and effectiveness of a separation agreement, including, among other things, a general release of claims, Mr. Ritter will be eligible to receive base salary continuation for six months in the event that his employment is terminated by us without cause. The receipt of the severance payments and benefits set forth above shall be conditioned upon Mr. Ritter not violating the terms of a restrictive covenant agreement between Mr. Ritter and Inotek.

Termination and Change of Control Benefits

Subject to the execution and effectiveness of a separation agreement, including, among other things, a general release of claims, and each named executive officer, excluding Dr. McVicar, not violating the terms of a restrictive covenant agreement, each named executive officer will be eligible to receive the payments and benefits set forth below in the event that such executive officer's employment is terminated by us without cause or the named executive officer terminates his or her employment with us for good reason, in either case within twelve months after a "change in control." The payments and benefits described below and due to each named executive officer other than Mr. Southwell are in addition to, not in lieu of, the payments set forth above next to such named executive officer's name. With respect to Mr. Southwell, the payments and benefits described below are in lieu of the payments set forth above next to Mr. Southwell's name.

- With respect to all named executive officers other than Mr. Southwell, all unvested stock options and other stock-based awards held by such named executive officer as of the date of the termination of such named executive officer's employment shall immediately accelerate and become fully vested as of the date of termination of such named executive officer.
- With respect to Mr. Southwell, a one-time lump payment equal to 18 months base salary within 45 days of termination.

Under the Transition Agreement, we have also agreed (i) to pay Dr. McVicar severance pay consisting of salary continuation at his final base salary rate, less applicable tax-related deductions and withholdings, effective for the twelve month period immediately following the Separation Date (the "Severance Pay Period") and (ii) to pay the same portion of the COBRA premium payment

reimbursements that we pay active employee for the same level of group medical and dental coverage as in effect for Dr. McVicar if he elects continuation of his COBRA coverage on the Separation Date until the end of the Severance Pay Period.

Equity Incentive Awards

Outstanding Equity Awards at Fiscal Year-End

The following table provides information concerning outstanding equity awards for each of our named executive officers as of December 31, 2016.

	Option Awards				Stock Awards	
Name	Number of securities underlying unexercised options exercisable	Number of securities underlying unexercised options unexercisable	Per share option exercise price ($)	Option expiration date	Number of securities that have not vested	Market value of securities that have not vested ($) (5)
David P. Southwell	232,456 (1)	166,041 (1)	4.342	8/28/2024	—	—
	68,750 (2)	81,250 (2)	5.03	6/23/2025	—	—
	—	215,000 (3)	7.56	3/21/2026	—	—
	—	—	—		350,000 (5)	2,135,000 (6)
Rudolf Baumgartner, M.D.	2,170 (4)	—	40.578	6/3/2017		
	197 (4)	—	40.578	3/20/2018		
	116,228 (1)	83,020 (1)	4.342	8/28/2024		
	34,370 (2)	40,630 (2)	5.03	6/23/2025		
	—	165,000 (3)	7.56	3/21/2026		
	—	—	—		120,000 (5)	732,000 (6)
William K. McVicar, Ph.D. (7)	1,269 (4)	—	40.58	9/18/2017		
	462 (4)	—	40.58	12/31/2018		
	115 (4)	—	40.58	3/20/2018		
	116,228 (1)	83,020 (1)	4.342	8/28/2024		
	34,370 (2)	40,630 (2)	5.03	6/23/2025		
	—	135,000 (3)	7.56	3/21/2026		
Dale Ritter	25,651 (1)	18,331 (1)	4.342	8/28/2024		
	11,450 (2)	13,550 (2)	5.03	6/23/2025		
	—	40,000 (3)	7.56	3/21/2026		

(1) These stock options were granted pursuant to our 2014 Stock Option and Incentive Plan (the “2014 Plan”) on August 28, 2014, have a ten-year term and vested 25% on the one-year anniversary of the grant date and the remaining 75% will vest equally over the following 36 monthly anniversaries.

(2) These stock options were granted pursuant to our 2014 Plan on June 24, 2015, have a ten-year term, and vested 25% on the one-year anniversary of our IPO and the remaining 75% will vest equally over the following 36 monthly anniversaries.

(3) These stock options were granted pursuant to our 2014 Plan on March 22, 2016, have a ten-year term, and will vest 25% on January 1, 2017 and the remaining 75% will vest equally over the following 36 monthly anniversaries.

(4) These stock options were granted pursuant to our 2004 Stock Option and Incentive Plan (the “2004 Plan”) and are fully vested.

(5) These restricted stock units were granted pursuant to our 2014 Plan on December 13, 2016 and were amended on January 23, 2017 to modify their vesting schedule. The restricted stock units were modified such that, instead of vesting subject to the achievement of certain performance criteria, the awards will vest in equal annual installments over four years from the date of grant, subject to the named executive officer’s continued service through such each date.

(6) The value of the restricted stock units reflected in the table is based on a price per share of $6.10, which was the closing price of our common stock as of December 30, 2016.

(7) Dr. McVicar ceased being an executive officer on October 4, 2016.

Employee Stock Purchase Plan

In November 2014, the Company’s Board of Directors adopted and the stockholders approved the 2014 Employee Stock Purchase Plan (the “ESPP”). The ESPP permits eligible employees to purchase shares of the Company’s common stock through payroll withholdings and pursuant to specific offerings of common stock. An eligible employee may contribute up to 10%, in full percentages, of gross wages, which are withheld from each payroll, to the ESPP. At the end of each offering, an ESPP participant

employee will purchase shares at 85% of the lower of the fair value of the Company's common stock on the first and last day of the offering with aggregate withholdings as of the end of the offering. The offerings commence on June 1 and December 1 and are six months in duration. A participant may reduce his or her withholdings as many times as he or she wishes and may increase his or her withholdings two times during an offering. The Company's Board of Directors has authorized the issuance of a number of shares of common stock issuable under the ESPP to the number that represents 1% of the Company's outstanding common stock outstanding immediately after the IPO, or 160,276 shares. The ESPP provides that the number of shares reserved and available for issuance under the ESPP shall be cumulatively increased each January 1, beginning on January 1, 2016, by the lesser of (i) 600,000 shares of common stock or (ii) the number of shares necessary to set the number of shares of Common Stock under the Plan at 1% percent of the outstanding number of shares as of January 1 of the applicable year. However, the Board of Directors reserves the right to determine that there will be no increase for any year or that any increase will be for a lesser number of shares. On January 1, 2017, the number of shares reserved and available for issuance under the ESPP was increased by 31,555 to 269,863 shares. During 2016, 5,790 shares and 20,135 shares of common stock were purchased by plan participants and issued by the Company pursuant to two offerings under the ESPP at a purchase price of $7.82 and $5.44 per share, respectively. Mr. Southwell purchased 2,765 shares at $5.44 per share. Dr. Baumgartner purchased 2,530 shares at $5.44 per share. Dr. McVicar purchased 1,092 shares at $7.82 per share. Mr. Ritter purchased 782 shares at $7.82 per share and 1,765 shares at $5.44 per share.

Inotek Pharmaceuticals Corporation 401(k) Profit-Sharing Plan (the "401(k) Plan")

The Company maintains the 401(k) Plan through which its employees who are not covered by a collective bargaining agreement and are not non-resident aliens may contribute a portion of their earnings on a tax-deferred basis, up to certain limitations specified by federal law. The Company may, in its sole discretion, make a matching contribution on behalf of a contributing employee. The Company has elected to match 100% of the first 3% of compensation contributed by an employee. All employee contributions are immediately vested. Matching contributions made by the Company vest based on years of service according to the following vesting schedule: less than one year, 0%; one year but less than two years, 25%; two years but less than three years, 50%; three years or more, 100%.

EQUITY COMPENSATION PLAN INFORMATION

The following sets forth the aggregate information of our equity compensation plans in effect as of December 31, 2016. Our equity plans consist of our 2014 Plan, our 2004 Plan and our ESPP.

Plan Category	Number of securities to be issued upon exercise of outstanding options, warrants and rights	Weighted-average exercise price of outstanding options, warrants and rights	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column (a))
	(a)	(b)	(c)
Equity compensation plans approved by security holders (1) (2)	3,145,458	$ 6.30	241,342
Equity compensation plans not approved by security holders	—	—	—
Total	3,145,458	$ 6.30	241,342

(1) No additional awards will be made under the 2004 Stock Option and Incentive Plan.

(2) Includes 470,000 Restricted Stock Units issued pursuant to the 2014 Plan. There is no exercise price associated with these restricted stock units and therefore the weighted average price of outstanding options, warrants and rights reflects only the weighted average exercise price of the 2,675,458 options outstanding at December 31, 2016 issued pursuant to the 2004 and 2014 Plans.

DIRECTOR COMPENSATION

Director Compensation Table

The following table presents the total compensation for each person who served as a member of our Board during 2016. Other than as set forth in the table and described more fully below, we did not pay any compensation, make any equity awards or non-equity awards to, or pay any other compensation to any of the non-employee members of our Board in 2016. David P. Southwell, who is also

our President and Chief Executive Officer, receives no compensation for his service as a director, and, consequently, is not included in this table.

Our Board adopted a formal director compensation policy for all of our non-employee directors that became effective upon the closing of our initial public offering.

2016 Director Compensation Table

Director name	Fees earned $ (8)	Option awards $ (6)	All other compensation ($)	Total ($)
Timothy Barberich	11,617	154,251 (1)	—	165,868
Carsten Boess	48,523	204,930 (2)	—	253,453
J. Martin Carroll	44,548	442,488 (3)	7,500 (7)	494,536
Ittai Harel	26,442	-	—	26,442
Paul G. Howes	38,915	58,288 (4)	—	97,203
A.N. “Jerry” Karabelas, Ph.D.	31,250	-	—	31,250
Patrick Machado	15,822	113,098 (5)	7,500 (7)	136,420
Isai Peimer	14,500	-	—	14,500
Gary Phillips, M.D.	41,123	58,288 (4)	—	99,411
Richard N. Spivey, PharmD, PhD	42,849	58,288 (4)	—	101,137
Martin Vogelbaum	25,240	-	—	25,240

(1) For Mr. Barberich, represents the grant date fair value of an initial grant of an option to purchase 24,000 shares of our common stock with an exercise price of $9.49 per share upon his becoming a director on September 28, 2016.

(2) For Mr. Boess, represents the grant date fair value of $146,642 of an initial grant of an option to purchase 24,000 shares of our common stock with an exercise price of $8.99 per share upon his becoming a director on January 11, 2016 and the grant date fair value of $58,288 of an option to purchase 12,000 shares of our common stock granted to each then-current non-employee director on June 23, 2016 with an exercise price of $7.61 per share.

(3) For Mr. Carroll, represents the grant date fair value of $123,691 of an initial grant of an option to purchase 24,000 shares of our common stock with an exercise price of $7.63 per share upon his becoming a director on April 1, 2016, the grant date fair value of $260,509 of an option to purchase 51,000 shares of our common stock upon his becoming chairman of the board on June 23, 2016, and the grant date fair value of $58,288 of an option to purchase 12,000 shares of our common stock granted to each then-current non-employee director on June 23, 2016 with an exercise price of $7.61 per share.

(4) For Mr. Howes, Dr. Phillips and Dr. Spivey, represents the grant date fair value of $58,288 of an option to purchase 12,000 shares of our common stock granted to each then-current non-employee director on June 23, 2016 with an exercise price of $7.61 per share.

(5) For Mr. Machado, represents the grant date fair value of an initial grant of an option to purchase 24,000 shares of our common stock with an exercise price of $6.91 per share upon his becoming a director on August 17, 2016.

(6) Reflects the grant date fair value of option awards, calculated in accordance with ASC Topic 718, disregarding the estimate on forfeitures. The assumptions we used for calculating grant date fair values are set forth in Note 8 of Notes to Consolidated Financial Statements in this Form 10-K.

(7) Represents consulting fees paid to Mr. Carroll and Mr. Machado prior to their becoming directors.

(8) Represents fees earned in 2016, a portion of which were paid in 2017.

As of December 31, 2016, total options shares held by board members are as follows: 24,000 shares for Mr. Barberich and Mr. Machado; 36,000 shares for Mr. Boess, Dr. Phillips and Dr. Spivey; 87,000 shares for Mr. Carroll; and 33,857 shares for Mr. Howes.

Post IPO Non-Employee Director Compensation

The Company adopted a non-employee director compensation policy that became effective upon the Company’s IPO in February 2015. The purpose of this policy is to provide a total compensation package that enables the Company to attract and retain, on a long-term basis, high-caliber directors who are not employees or officers of the Company. During 2016, for service on the board of directors, annual cash retainers were paid as follows: for board members, $35,000, for the non-executive chairperson, $65,000. In 2017, for service on the board of directors, annual cash retainers will be paid as follows: for board members, $50,000, for the non-executive chairperson, $92,850. In addition to cash retainers for service on the board of directors, additional cash retainers are paid for service on committees of the board of directors. For service on the Audit Committee, annual cash retainers will be paid as follows: for committee members, $7,500, for the chairperson, $15,000. For service on the Compensation Committee, annual cash retainers will be

paid as follows: for committee members, $5,000, for the chairperson, $10,000. For service on the Nominating and Corporate Governance Committee, annual cash retainers will be paid as follows: for committee members, $3,000, for the chairperson, $7,500.

In addition, each new non-employee director upon his/her election to the Board will receive a one-time option grant to purchase shares of the Company's common stock, par value $0.01 per share in such amount and on such terms as authorized by the Board, or by a committee appointed by the Board. On the date of each Annual Meeting of Stockholders, an annual option will be granted to each non-employee director serving on the Board immediately following the Company's annual meeting of stockholders to purchase shares of common stock in such amount and on such terms as authorized by the Board, or by a committee appointed by the Board.

All of the foregoing option grants will have an exercise price equal to the fair market value of a share of common stock on the date of grant.

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

PRINCIPAL STOCKHOLDERS

The following table sets forth certain information known to us regarding beneficial ownership of our capital stock as of February 15, 2017 for:

- each person, or group of affiliated persons, known by us to be the beneficial owner of more than 5% of our capital stock;
- our named executive officers;
- each of our other directors; and
- all executive officers and directors as a group.

Beneficial ownership is determined in accordance with the rules of the SEC. A person is deemed to be a beneficial holder of our common stock if that person has or shares voting power, which includes the power to vote or direct the voting of our common stock, or investment power, which includes the power to dispose of or to direct the disposition of such capital stock. Except as noted by footnote, and subject to community property laws where applicable, we believe based on the information provided to us that the persons and entities named in the table below have sole voting and investment power with respect to all common stock shown as beneficially owned by them.

The table lists applicable percentage ownership based on 26,986,318 shares of common stock outstanding as of February 15, 2017 and excludes (i) 6,483,791 shares of common stock issuable upon conversion of the 2021 Convertible Notes, (ii) 2,675,458 shares of common stock issuable upon the exercise of stock options outstanding as of February 15, 2017, at a weighted-average exercise price of $6.30 per share; (iii) 56,408 shares of common stock issuable upon the exercise of warrants outstanding as of February 15, 2017, which have an exercise price of $6.204 per share and (iv) 1,401,000 unvested Restricted Stock Units outstanding as of February 15, 2017. Shares of common stock that may be acquired by an individual or group within 60 days of February 15, 2017, pursuant to the exercise of options, warrants or other rights, are deemed to be beneficially owned by the persons holding these options for the purpose of computing percentage ownership of that person, but are not treated as outstanding for the purpose of computing any other person's ownership percentage.

Unless otherwise noted below, the address of each person listed on the table is c/o Inotek Pharmaceuticals Corporation, 91 Hartwell Avenue, Second Floor, Lexington, MA 02421.

Name and address of beneficial owner	Number of Shares Beneficially Owned	Percent of Class
5% Stockholders		
OrbiMed Entities (1)	2,788,111	10.0%
Rho Ventures Entities (2)	2,627,790	9.7%
Prudential Financial, Inc. (3)	1,981,692	7.3%
MedImmune Ventures, Inc. (4)	1,917,906	7.1%
Citadel Entities (5)	1,917,020	6.6%
Care Capital Entities (6)	1,519,647	5.6%
Great Point Partners, LLC (7)	1,500,000	5.6%
Named executive officers and directors		
David P. Southwell (8)	465,439	1.7%
Rudolf Baumgartner, M.D. (9)	353,980	1.3%
William K. McVicar, Ph.D. (10)	323,337	1.2%
Dale Ritter (11)	59,046	*
Timothy Barberich	—	*
Carsten Boess (12)	16,500	*
J. Martin Carroll (13)	25,000	*
Paul G. Howes (14)	138,506	*
Patrick Machado	—	*
Gary Phillips, M.D. (15)	18,000	*
Richard N. Spivey, Pharm.D., Ph.D. (16)	19,500	*
All directors and executive officers as a group (11 persons) (17)	**1,419,308**	**5.1%**

* represents beneficial ownership of less than one percent.

(1) Based on Schedule 13G filed with the SEC on February 13, 2017, consists of (a) 879,530 shares of common stock beneficially owned by OrbiMed Advisors LLC (“OrbiMed Advisors”), (b) 399,202 shares of common stock issuable upon conversion of convertible notes beneficially owned by OrbiMed Advisors (c) 1,035,327 shares of common stock held by OrbiMed Capital LLC (“OrbiMed Capital”) and (d) 474,052 shares of common stock upon conversion of convertible notes held by OrbiMed Capital. Samuel D. Isaly is a control person of OrbiMedAdvisors and OrbiMed Capital. The principal address of the beneficial owners is 601 Lexington Avenue, 54th Floor, New York, NY 10022.

(2) Based on Schedule 13G filed with the SEC on February 12, 2016, consists of (a) 892,415 shares beneficially owned by Rho Ventures IV (QP), L.P. (“Rho QP”), (b) 930,029 shares beneficially owned by Rho Ventures IV GmbH & Co. BETEILIGUNGS KG (“Rho GmbH”), (c) 636,496 shares beneficially owned by Rho Ventures IV Holdings LLC (“Rho Holdings”), and (d) 168,850 shares beneficially owned by Rho Ventures IV, L.P. (“Rho IV”). The voting and dispositive decisions with respect to the shares held by Rho IV, Rho Holdings, and Rho QP are made by the following managing members of their general partner or managing member, Rho Management Ventures IV, L.L.C.: Mark Leschly, Habib Kairouz and Joshua Ruch. The voting and dispositive decisions with respect to the shares held by Rho GmbH are made by the following managing directors of its general partner, Rho Capital Partners Verwaltungs GmbH: Mark Leschly, Habib Kairouz and Joshua Ruch. The address for the Rho Venture Entities is 152 West 57th Street, 23rd Floor, New York, New York 10019.

(3) Based on Schedules 13G/A filed with the SEC on January 24, 2017 and February 3, 2017, consists of (i) 1,980,842 shares of common stock held directly by Jennison Associates LLC (“Jennison”) and (ii) 850 shares of common stock held directly by Quantitative Management Associates LLC (“Quantitative”). Jennison and Quantitative are each a wholly-owned subsidiary of Prudential Financial, Inc., and over which Prudential Financial, Inc. has sole voting and dispositive power. The principal business address of the beneficial owner is 751 Broad Street, Newark, NJ 07102-3777.

(4) Based on Schedule 13G filed with the SEC on February 16, 2016, consists of 1,917,906 shares beneficially owned by MedImmune Ventures, Inc. The voting and investment power of the shares held by MedImmune Ventures, Inc. is determined by Ron Laufer, Senior Managing Director of MedImmune Ventures, Inc. Isai Peimer, a former member of our Board of Directors, was a Managing Director at MedImmune Ventures, Inc. The address of MedImmune Ventures, Inc. is 1 MedImmune Way, Gaithersburg, Maryland 20878.

(5) Based on Schedule 13G/A filed with the SEC on February 14, 2017, consists of 1,917,020 shares of common stock issuable upon conversion of convertible notes beneficially owned by Citadel Equity Fund Ltd. (“CEF”), Citadel Clearing LLC (“CCLC”) and Citadel Securities LLC (“Citadel Securities”). Citadel Advisors LLC (“Citadel Advisors”) is the portfolio manager of CEF. Citadel Advisors Holdings II LP (“CAH2”) is the managing member of Citadel Advisors. CLP Holdings Six LLC (“CLP6”) is

the portfolio manager of CCLC. CALC III LP if the non-member manager of Citadel Securities and CLP6. Citadel GP LLC ("CGP") is the general partner of CALC3 and CAH2. Kenneth Griffin is the President and Chief Executive Officer of, and owns a controlling interest in, CGP. The address of the principal business office of Citadel is c/o Citadel LLC, 131 S. Dearborn Street, 32nd Floor, Chicago, Illinois 60603.

(6) Based on Schedule 13D/A filed with the SEC on February 10, 2017, consists of (a) 1,494,688 shares beneficially owned by Care Capital Investments III, L.P ("Investments III") and (b) 24,959 shares beneficially owned by Care Capital Offshore Investments III, LP. ("Offshore III"). The voting and disposition of the shares held by Investments III and Offshore III is determined by the following managing members of their general partner, Care Capital III, LLC: A.N. "Jerry" Karabelas, Ph.D., a former member of our Board of Directors, Jan Leschly, Richard Markham and David R. Ramsay. The address of the Care Capital Entities is 47 Hull Street, Suite 310, Princeton, New Jersey 08540.

(7) Based on Schedule 13G/A filed with the SEC on February 14, 2017, consists of (a) 421,498 shares of common stock beneficially owned by Biomedical Value Fund, L.P. ("BVF") (the "BVF Shares"), (b) 607,500 shares of common stock beneficially owned by Biomedical Offshore Value Fund, Ltd. ("BOVF") (the "BOVF Shares") and (c) 471,002 shares of common stock beneficially owned by GEF-SMA, LP ("GEF-SMA") (the "GEF-SMA Shares"). Great Point Partners, LLC ("Great Point") is the investment manager of BVF, BOVF and GEF-SMA, and by virtue of such status may be deemed to be the beneficial owner of the BVF Shares, BOVF Shares and GEF-SMA Shares. Each of Dr. Jeffrey R. Jay, M.D., as senior managing member of Great Point, and Mr. David Kroin, as special managing member of Great Point, has voting and investment power with respect to the BVF Shares, BOVF Shares and GEF-SMA Shares, and therefore may be deemed to be the beneficial owner of the BVF Shares, BOVF Shares and GEF-SMA Shares. Great Point, Dr. Jay and Mr. Kroin disclaim beneficial ownership of the BVF Shares, the BOVF Shares and the GEF-SMA Shares described above, except to the extent of their respective pecuniary interests. The address of Great Point is 165 Mason Street, 3rd Floor, Greenwich, CT 06830.

(8) Consists of (i) 62,765 shares of common stock and (ii) 402,674 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(9) Consists of (i) 132,315 shares of common stock and (ii) 221,665 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(10) Consists of (i) 111,568 shares of common stock and (ii) 211,769 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017. Dr. McVicar ceased being an executive officer on October 4, 2016.

(11) Consists of (i) 5,138 shares of common stock and (ii) 53,908 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(12) Consists of 16,500 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(13) Consists of (i) 10,000 shares of common stock and (ii) 15,000 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(14) Consists of (i) 101,489 shares of common stock and (ii) 37,017 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(15) Consists of 18,000 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(16) Consists of 19,500 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

(17) Consists of (i) 423,275 shares of common stock and (ii) 996,033 shares of common stock issuable upon the exercise of options exercisable within 60 days after February 15, 2017.

Equity Compensation Plan Information

For information concerning securities authorized for issuance under our equity compensation plans, see "Item 11 – Equity Compensation Plan Information" of this Form 10-K.

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

Other than compensation arrangements, we describe below transactions and series of similar transactions, since January 1, 2014, which includes our last three full fiscal years, to which we were a party or will be a party, in which:

- the amounts involved exceeded or will exceed $120,000; and
- any of our directors, executive officers or holders of more than 5% of our capital stock, or any member of the immediate family of the foregoing persons, had or will have a direct or indirect material interest.

Compensation arrangements for our directors and named executive officers are described elsewhere in this prospectus and other documents incorporated by reference herein.

Sales and Purchases of Securities

In December 2014, we sold subordinated convertible promissory notes, or the "2014 bridge notes", in the aggregate original principal amount of $2.0 million to existing stockholders. As consideration for our issuance of the 2014 bridge notes, each investor paid us an amount equal to the original principal amount of the note issued to the investor. The 2014 bridge notes mature on June 30, 2015, accrue interest at the rate of 8% per annum and are subordinate to all other senior indebtedness of the Company. As of the date of this prospectus, the aggregate outstanding principal and accrued interest under the 2014 bridge notes is approximately $2.0 million. Upon the closing of our initial public offering, all outstanding principal and accrued interest of the 2014 bridge notes, automatically converted into common stock at the initial public offering price. The following table summarizes the participation in the 2014 bridge notes financing by any of our directors, executive officers, holders of more than 5% of our voting securities, or any member of the immediate family of the foregoing persons.

Name	Principal Amount of Subordinated Convertible Promissory Note
Devon Park Bioventures, L.P. (1)	$ 626,942.90
Rho Ventures IV, L.P. (2)	$ 27,797.11
Rho Ventures IV (QP), L.P. (2)	$ 146,910.56
Rho Ventures IV GmbH & Co. Beteiligungs KG (2)	$ 153,102.29
Rho Ventures IV Holdings LLC (2)	$ 104,780.66
Care Capital Investments III, LP (3)	$ 369,989.00
Care Capital Offshore Investments III, LP (3)	$ 6,178.93
MedImmune Ventures, Inc. (4)	$ 338,551.12
Pitango Venture Capital Fund IV, L.P. (5)	$ 220,975.53
Pitango Venture Capital Principals Fund IV, L.P. (5)	$ 4,771.90

(1) Devang V. Kantesaria, a former member of our Board of Directors, is a managing member of Devon Park Associates, LLC, of which Devon Park Bioventures, L.P., a former 5% shareholder, is an affiliated fund.
(2) Martin Vogelbaum, a former member of our Board of Directors was a Partner at Rho, of which the Rho Venture Entities are affiliated funds.
(3) A.N. "Jerry" Karabelas, a former member of our Board of Directors, is a managing member at Care Capital II, LLC and Care Capital III, LLC, of which the Care Capital Entities are affiliated funds.
(4) Isai Peimer, a former member of our Board of Directors, was a Managing Director at MedImmune Ventures, Inc.
(5) Ittai Harel, a former member of our Board of Directors, is a general partner with Pitango Venture Capital, of which the Pitango Venture Capital Fund Entities, former 5% shareholders, are affiliated funds.

Agreements With Our Stockholders

In connection with our preferred stock financings, we entered into a third amended and restated investor rights agreement, or Investor Rights Agreement, and a third amended and restated stockholders agreement, as amended, or Stockholders Agreement, in each case, with the purchasers of our preferred stock and, in the case of the stockholders agreement, certain holders of our common stock.

The rights under each of the Investor Rights Agreement and the Stockholders Agreement terminated upon the closing of our initial public offering, other than certain registration rights for certain holders of our preferred stock.

Employment Agreements

We have employment agreements with our executive officers, which provide for certain salary, bonus, stock option and severance compensation.

Indemnification Agreements

Our Seventh Amended and Restated Certificate of Incorporation and our bylaws, as amended, provide that we shall indemnify our directors and officers to the fullest extent permitted by law. In addition, we have previously entered into and intend to enter into new agreements to indemnify our directors and executive officers. These agreements will, among other things, indemnify these individuals for certain expenses (including attorneys' fees), judgments, fines and settlement amounts reasonably incurred by such

person in any action or proceeding, including any action by or in our right, on account of any services undertaken by such person on behalf of us or that person's status as a member of our Board of Directors.

Director Independence

Information about director independence is incorporated herein by reference to Item 11 of Part III of this Annual Report on Form 10-K.

Item 14. Principal Accountant Fees and Services

Our audit committee pre-approves all audit and permissible non-audit services provided by RSM US LLP (formerly McGladrey LLP). These services may include audit services, audit-related services, tax services and other services. Pre-approval may be given as part of the audit committee's approval of the scope of the engagement of the independent registered public accounting firm or on an individual case-by-case basis. All of the services described below were approved by our audit committee.

In 2014, we retained RSM US LLP (formerly McGladrey LLP) to provide audit services for the fiscal years ended December 31, 2014, 2013, and 2012, and for services in connection with our IPO which took place in February 2015. In the table below, audit fees reflect fees for audit services for the years ended December 31, 2016 and 2015. Audit-Related Fees for 2015 reflect fees from our IPO-related and Follow-On offering services performed in 2015. Audit-Related Fees for 2016 primarily reflect fees from services performed on our registration statement on Form S-3.

	2016	2015
Audit Fees	$ 162,950	$ 162,900
Audit-Related Fees	67,300	148,000
Tax Fees	36,000	—
All Other Fees	—	—
Total	$ 266,250	$ 310,900

PART IV

Item 15. Exhibits, Financial Statements and Schedules

(a) The following documents are filed as part of this report:

(1) Financial Statements:

(2) Financial Statement Schedules:

All financial statement schedules have been omitted because they are not applicable, not required or the information required is shown in the financial statements or the notes thereto.

(3) Exhibits:

The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following our consolidated financial statements. The Exhibit Index is incorporated herein by reference.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of the 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, in the City of Lexington, Commonwealth of Massachusetts, on March 16, 2017.

Inotek Pharmaceuticals Corporation

By: /s/ David P. Southwell
David P. Southwell
President, Chief Executive Officer and Director

POWER OF ATTORNEY

Each person whose individual signature appears below hereby constitutes and appoints David P. Southwell and Dale Ritter, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

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

Name	Title	Date
/s/ David P. Southwell David P. Southwell	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 16, 2017
/s/ Dale Ritter Dale Ritter	Vice President–Finance *(Principal Financial and Accounting Officer)*	March 16, 2017
/s/ J. Martin Carroll J. Martin Carroll	Director	March 16, 2017
/s/ Timothy Barberich Timothy Barberich	Director	March 16, 2017
/s/ Carsten Boess Carsten Boess	Director	March 16, 2017
/s/ Paul G. Howes Paul G. Howes	Director	March 16, 2017
/s/ Patrick Machado Patrick Machado	Director	March 16, 2017
/s/ Gary Phillips, M.D. Gary Phillips, M.D.	Director	March 16, 2017
/s/ Richard N. Spivey, PharmD, PhD Richard N. Spivey, PharmD, PhD	Director	March 16, 2017

Inotek Pharmaceuticals Corporation

Index to Financial Statements

Contents

Report of Independent
Registered Public Accounting Firm

To the Board of Directors and Stockholders
Inotek Pharmaceuticals Corporation

We have audited the accompanying consolidated balance sheets of Inotek Pharmaceuticals Corporation as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, changes in redeemable convertible preferred stock and stockholders' equity (deficit) and cash flows for the years then ended. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, 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. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Inotek Pharmaceuticals Corporation as of December 31, 2016 and 2015, and the results of its operations and its cash flows for the years then ended in conformity with U.S. generally accepted accounting principles.

/s/ RSM US LLP

Boston, Massachusetts
March 16, 2017

Inotek Pharmaceuticals Corporation

Consolidated Balance Sheets
(in thousands, except share and per share amounts)

	December 31, 2016	December 31, 2015
Assets		
Current assets:		
Cash and cash equivalents	$ 29,798	$ 80,042
Short-term investments	96,675	31,238
Prepaid expenses and other current assets	1,876	1,086
Total current assets	128,349	112,366
Property and equipment, net	1,130	812
Other assets	168	143
Total assets	$ 129,647	$ 113,321
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,592	$ 1,633
Accrued expenses and other current liabilities	4,416	2,508
Accrued interest	1,204	—
Total current liabilities	7,212	4,141
2021 Convertible Notes, net of issuance costs	48,960	—
Other long-term liabilities	307	367
Total liabilities	56,479	4,508
Commitments and Contingencies (Note 9)		
Stockholders' equity:		
Preferred Stock, $0.001 par value: 5,000,000 shares authorized and no shares issued or outstanding	—	—
Common stock, $0.01 par value: 120,000,000 shares authorized at December 31, 2016 and December 31, 2015; 26,986,318 shares and 26,423,394 shares issued and outstanding at December 31, 2016 and December 31, 2015, respectively	270	264
Additional paid-in capital	311,829	304,583
Accumulated deficit	(238,877)	(196,023)
Accumulated other comprehensive loss	(54)	(11)
Total stockholders' equity	73,168	108,813
Total liabilities and stockholders' equity	$ 129,647	$ 113,321

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

Inotek Pharmaceuticals Corporation

Consolidated Statements of Operations
(in thousands, except share and per share amounts)

	For the Years Ended December 31,	
	2016	2015
Operating expenses:		
Research and development	$ (31,985)	$ (12,554)
General and administrative	(9,894)	(7,842)
Loss from operations	(41,879)	(20,396)
Interest expense	(1,418)	(1,230)
Interest income	443	89
Loss on extinguishment of debt	—	(4,399)
Change in fair value of warrant liabilities	—	267
Change in fair value of Convertible Bridge Notes redemption rights derivative	—	480
Change in fair value of 2020 Convertible Notes derivative liability	—	(42,793)
Net loss	$ (42,854)	$ (67,982)
Net loss per share attributable to common stockholders—basic and diluted	$ (1.60)	$ (3.72)
Weighted-average number of shares outstanding—basic and diluted	26,735,175	18,311,333

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

Inotek Pharmaceuticals Corporation

Consolidated Statements of Comprehensive Loss
(in thousands)

	For the Years Ended December 31,	
	2016	2015
Net loss	$ (42,854)	$ (67,982)
Other comprehensive loss:		
Net unrealized loss on marketable securities	(43)	(11)
Total comprehensive loss	$ (42,897)	$ (67,993)

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

Inotek Pharmaceuticals Corporation

Consolidated Statements of Changes in Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share amounts)

	Series AA Redeemable Convertible Stock		Series X Redeemable Convertible Stock		Common Stock		Additional Paid in	Accumulated	Accumulated Other Comprehensive	
	Shares	Amount	Shares	Amount	Shares	Par value	Capital	Deficit	Loss	Total
Balances at December 31, 2014	24,057,013	$ 46,253	1,892,320	$ 548	1,020,088	$ 10	$ 76,472	$ (128,041)	$ —	$ (51,559)
Stock-based compensation	—	—	—	—	—	—	2,380	—	—	2,380
Accretion of Series AA preferred stock to redemption value	—	131	—	—	—	—	(131)	—	—	(131)
Issuance of common stock upon initial public offering, net of $5,303 in offering costs	—	—	—	—	6,966,333	70	36,425	—	—	36,495
Conversion of Series AA preferred stock into common stock upon initial public offering	(24,057,013)	(46,384)	—	—	7,536,331	75	46,309	—	—	46,384
Conversion of Series X preferred stock into common stock upon initial public offering	—	—	(1,892,320)	(548)	466,319	5	543	—	—	548
Conversion of Convertible Bridge Notes into common stock upon initial public offering	—	—	—	—	337,932	3	2,024	—	—	2,027
Reclassification of fair value of warrant liability to equity upon initial public offering	—	—	—	—	—	—	215	—	—	215
Common stock issued pursuant to stock option plans	—	—	—	—	9,857	—	43	—	—	43
Common stock issued pursuant to employee stock purchase plan	—	—	—	—	13,143	—	63	—	—	63
Conversion of 2020 Convertible Notes into common stock	—	—	—	—	3,863,391	39	66,337	—	—	66,376
Issuance of common stock upon secondary public offering	—	—	—	—	6,210,000	62	73,903	—	—	73,965
Unrealized comprehensive loss on marketable securities	—	—	—	—	—	—	—	—	(11)	(11)
Net loss	—	—	—	—	—	—	—	(67,982)	—	(67,982)
Balances at December 31, 2015	—	—	—	—	26,423,394	264	304,583	(196,023)	(11)	108,813
Stock-based compensation	—	—	—	—	—	—	2,909	—	—	2,909
Stock options exercised	—	—	—	—	54,310	1	190	—	—	191
Common stock issued pursuant to employee stock purchase plan	—	—	—	—	25,925	—	155	—	—	155
Issuance of common stock, net of $403 in offering costs	—	—	—	—	482,689	5	3,992	—	—	3,997
Unrealized comprehensive loss on marketable securities	—	—	—	—	—	—	—	—	(43)	(43)
Net loss	—	—	—	—	—	—	—	(42,854)	—	(42,854)
Balances at December 31, 2016	—	$ —	—	$ —	26,986,318	$ 270	$ 311,829	$ (238,877)	$ (54)	$ 73,168

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

Inotek Pharmaceuticals Corporation

Consolidated Statements of Cash Flows
(in thousands)

	For the Years Ended December 31,	
	2016	**2015**
Cash flows from operating activities:		
Net loss	$ (42,854)	$ (67,982)
Adjustments to reconcile net loss to cash used in operating activities:		
Noncash interest expense	222	1,132
Noncash rent expense	(60)	(20)
Loss on extinguishment of debt	—	4,239
Amortization of premium on marketable securities	225	75
Depreciation	169	45
Change in fair value of warrant liabilities	—	(267)
Change in fair value of Convertible Bridge Notes redemption rights derivative	—	(480)
Change in fair value of 2020 Convertible Notes derivative liability	—	42,793
Stock-based compensation	2,909	2,380
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(948)	(1,256)
Accounts payable	(41)	487
Accrued expenses and other current liabilities	3,112	1,438
Net cash used in operating activities	(37,266)	(17,416)
Cash flows from investing activities:		
Purchases of short-term investments	(122,277)	(33,693)
Proceeds from the maturities of short-term investments	56,705	2,430
Purchase of property and equipment	(487)	(412)
Net cash used in investing activities	(66,059)	(31,675)
Cash flows from financing activities:		
Proceeds from issuance of 2021 Convertible Notes	52,000	—
Payments of 2021 Convertible Notes issuance costs	(3,262)	—
Net proceeds from issuance of common stock in initial public offering	—	38,085
Proceeds from issuance of 2020 Convertible Notes in initial public offering	—	21,000
Payments of 2020 Convertible Notes issuance costs	—	(1,841)
Net proceeds from issuance of common stock	3,997	73,965
Proceeds from the issuance of common stock pursuant to stock option plan	191	43
Proceeds from the issuance of common stock pursuant to employee stock purchase plan	155	63
Principal payments on notes payable	—	(5,800)
Net cash provided by financing activities:	53,081	125,515
Net change in cash and cash equivalents	(50,244)	76,424
Cash and cash equivalents, beginning of period	80,042	3,618
Cash and cash equivalents, end of period	$ 29,798	$ 80,042
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ —	$ 89
Supplemental disclosure of noncash investing and financing activities:		
Acquisition of leasehold improvements	$ —	$ 445
Conversion of Series AA preferred stock into common stock upon initial public offering	$ —	$ 46,384
Conversion of Series X preferred stock into common stock upon initial public offering	$ —	$ 548
Conversion of Convertible Bridge Notes into common stock upon initial public offering	$ —	$ 2,027
Conversion of 2020 Convertible Notes into common stock	$ —	$ 66,376
Accretion of Series AA preferred stock to redemption value	$ —	$ 131
Reclassification of fair value of warrant liability to equity upon initial public offering	$ —	$ 215
Reclassification of deferred public offering costs to stockholders' equity	$ —	$ 1,590
Reclassification of deferred public offering costs to other assets	$ —	$ 256
Net unrealized loss on marketable securities	$ 43	$ 11

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

1. Organization and Operations

Inotek Pharmaceuticals Corporation (the "Company") is a clinical-stage biopharmaceutical company developing molecules with novel mechanisms of action to address significant diseases of the eye. The Company's business strategy is to develop and progress its product candidates through human clinical trials. The Company's headquarters are located in Lexington, Massachusetts.

The Company has devoted substantially all of its efforts to research and development, including clinical trials of its product candidates. The Company has not completed the development of any product candidates. The Company has no current source of revenue to sustain present activities and does not expect to generate revenue until and unless the Company receives regulatory approval of and successfully commercializes its product candidates. The Company is subject to a number of risks and uncertainties similar to those of other life science companies developing new products, including, among others, the risks related to the necessity to obtain adequate additional financing, to successfully develop product candidates, to obtain regulatory approval of products candidates, to comply with government regulations, to successfully commercialize its potential products, to the protection of proprietary technology and to the dependence on key individuals.

In August 2016, the Company closed an underwritten public offering of $52,000 aggregate principal amount of 5.75% Convertible Senior Notes due 2021, including $2,000 from an exercise of the underwriters' overallotment option, (the "2021 Convertible Notes"), and received net proceeds of $48,738 after deducting underwriting discounts and offering-related costs (see Note 5).

In April 2016, the Company filed a registration statement on Form S-3 containing two prospectuses: (i) a base prospectus which covers the offering, issuance and sale of up to $200,000 in the aggregate of an indeterminate number of shares of common stock and preferred stock, such indeterminate principal amount of debt securities and such indeterminate number of warrants and units; and (ii) a sales agreement prospectus covering the offering, issuance and sale of up to a maximum aggregate offering price of $50,000 of the Company's common stock that may be issued and sold under an at-the-market sales agreement with Cowen and Company, LLC (the "ATM"). The $50,000 of common stock that may be issued and sold under the ATM reduces the available balance under the base prospectus by the amount issued. During the year ended December 31, 2016, the Company sold 482,689 shares of common stock and received net proceeds of $3,997, pursuant to the ATM. At December 31, 2016, $45,599 was available for sale of common stock under the ATM.

In the first quarter of 2015, the Company completed its initial public offering (the "IPO") of (i) 6,966,333 shares of common stock, including 299,333 shares from an exercise of the underwriters' overallotment option at a price of $6.00 per share and (ii) $21,000 aggregate principal amount of 5.0% Convertible Senior Notes due 2020 (the "2020 Convertible Notes"), including $1,000 from an exercise of the underwriters' overallotment option. Existing stockholders and their affiliated entities purchased approximately 3,005,000 shares of common stock issued in the IPO at the same terms. The Company received net proceeds of $36,495, after deducting underwriting discounts and offering-related costs, from its equity issuances and $18,903 in net proceeds, after deducting underwriting discounts and offering-related costs, from its debt issuances.

In July and August 2015, holders of $21,000 principal amount of the 2020 Convertible Notes elected to convert the principal into 3,333,319 shares of common stock. In addition, the Interest Make-Whole Payment (see Note 5) was settled with shares of common stock, at the election of the Company, resulting in the issuance of 530,072 additional shares of common stock.

In August 2015, the Company completed an underwritten public offering of its common stock (the "Follow-on Offering"). The Company issued 6,210,000 shares of its common stock at a price of $12.75 per share, including 810,000 shares from the underwriters' full exercise of their overallotment option, and received net proceeds of $73,965, after deducting underwriting discounts and offering-related costs.

Prior to this the Company has funded its operations primarily through the sale of preferred stock and issuance of convertible promissory notes and notes payable. As of December 31, 2016, the Company had an accumulated deficit of $238,877 and $126,473 of cash, cash equivalents and short-term investments.

The Company will need to expend substantial resources for research and development, including costs associated with the clinical testing of its product candidates and will need to obtain additional financing to fund its operations and to conduct trials for its product candidates. If such products were to receive regulatory approval, the Company would need to prepare for the potential commercialization of its product candidates and fund the commercial launch and continued marketing of its products.

The Company will require additional funding in the future and may not be able to raise such additional funds. The Company expects losses will continue as it conducts research and development activities. The Company will seek to finance future cash needs through public or private equity offerings, license agreements, debt financings, collaborations, strategic alliances, or any combination thereof. The incurrence of indebtedness would result in increased fixed payment obligations and could also result in restrictive covenants, such as limitations on our ability to incur additional debt, limitations on the Company's ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact the ability of the Company to conduct its business. If adequate funds are not available, the Company would delay, reduce or eliminate research and development programs and reduce administrative expenses. The Company may seek to access the public or private capital markets whenever conditions are favorable, even if it does not have an immediate need for additional capital at that time. In addition, if the Company raises additional funds through collaborations, strategic alliances or licensing arrangements with third parties, it may have to relinquish valuable rights to its technologies, future revenue streams or product candidates or to grant licenses on terms that may not be favorable to it. If the Company is unable to raise sufficient funding, it may be unable to continue to operate. There is no assurance that the Company will be successful in obtaining sufficient financing on acceptable terms and conditions to fund continuing operations, if at all. The failure of the Company to obtain sufficient funds on acceptable terms when needed could have a material adverse effect on the Company's business, results of operations and financial condition.

2. Significant Accounting Policies

Basis of Presentation—The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). The consolidated financial statements reflect the operations of the Company and its wholly-owned subsidiaries, Inotek Securities Corporation and Inotek Ltd. All significant intercompany balances and transactions have been eliminated in consolidation.

Segment Reporting—Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment.

Use of Estimates—The preparation of 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 financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from these estimates. Significant items subject to such estimates and assumptions include the valuation of stock options used for the calculation of stock-based compensation, fair value of warrant liabilities and other derivative instruments, and determination of accruals related to research and clinical development.

Comprehensive loss—Comprehensive loss is defined as the change in equity of a business enterprise during a period from transactions, and other events and circumstances from non-owner sources, and currently consists of net loss and changes in unrealized gains and losses on short-term investments. Accumulated other comprehensive loss consists entirely of unrealized gains and losses from short-term investments as of December 31, 2016 and 2015.

Cash and Cash Equivalents—Cash and cash equivalents consist of bank deposits, certificates of deposit and money market accounts. Cash equivalents are carried at cost which approximates fair value due to their short-term nature and which the Company believes do not have a material exposure to credit risk. The Company considers all highly liquid investments with maturities of three months or less at the date of purchase to be cash equivalents.

The Company maintains its cash and cash equivalent balances in the form of money market, savings or operating accounts with financial institutions that management believes are creditworthy. The Company's cash and cash equivalent accounts, at times, may exceed federally insured limits. The Company has not experienced any losses in such accounts. The Company believes it is not exposed to any significant credit risk on cash and cash equivalents.

Short-term investments—Short-term investments consist of investments in certificates of deposit, agency bonds and United States Treasury securities. Management determines the appropriate classification of these securities at the time they are acquired and evaluates the appropriateness of such classifications at each balance sheet date. The Company classifies its short-term investments as available-for-sale pursuant to Financial Accounting Standards Board ("FASB") Accounting Standard Codification ("ASC") 320, *Investments—Debt and Equity Securities*. Short-term investments are recorded at fair value, with unrealized gains and losses included as a component of accumulated other comprehensive loss in stockholders' equity and a component of total comprehensive loss, until

realized. Realized gains and losses are included in investment income on a specific-identification basis. There were no realized gains or losses on short-term investments for the years ended December 31, 2016 and 2015. There was $43 and $11 of net unrealized losses on short-term investments for years ended December 31, 2016 and 2015, respectively.

The Company reviews short-term investments for other-than-temporary impairment whenever the fair value of a short-term investment is less than the amortized cost and evidence indicates that a short-term investment's carrying amount is not recoverable within a reasonable period of time. Other-than-temporary impairments of investments are recognized in the statements of operations if the Company has experienced a credit loss, has the intent to sell the short-term investment, or if it is more likely than not that the Company will be required to sell the short-term investment before recovery of the amortized cost basis. Evidence considered in this assessment includes reasons for the impairment, compliance with the Company's investment policy, the severity and the duration of the impairment and changes in value subsequent to the end of the period.

Short-term investments at December 31, 2016 consist of the following:

	Cost Basis	Unrealized Gains	Unrealized Losses	Fair Value
	(in thousands)			
Current:				
Certificates of deposit	$ 22,046	$ —	$ —	$ 22,046
Agency bonds	5,917	—	(4)	5,913
United States Treasury securities	68,766	1	(51)	68,716
	$ 96,729	$ 1	$ (55)	$ 96,675

Short-term investments at December 31, 2015 consist of the following:

	Cost Basis	Unrealized Gains	Unrealized Losses	Fair Value
	(in thousands)			
Current:				
Certificates of deposit	$ 16,160	$ —	$ —	$ 16,160
Agency bonds	10,036	—	(5)	10,031
United States Treasury securities	5,053	—	(6)	5,047
	$ 31,249	$ —	$ (11)	$ 31,238

At December 31, 2016 and 2015, all short-term investments held by the Company had contractual maturities of less than one year. The Company evaluated its securities for other-than-temporary impairment and determined that no such impairment existed at December 31, 2016 and 2015.

Property and Equipment—Property and equipment are stated at cost. Expenditures for repairs and maintenance are charged to expense as incurred. Upon retirement or sale, the cost of the assets disposed of and the related accumulated depreciation are eliminated from the accounts and any resulting gain or loss is reflected in the consolidated statement of operations. Depreciation and amortization is provided using the straight-line method over the estimated useful lives of the assets, which are as follows:

Asset Classification	Estimated Useful Life
Computer hardware and software	3 - 5 years
Laboratory equipment	5 years
Office equipment	5 years
Leasehold improvements	Shorter of useful life or remaining life of lease

Debt Issuance Costs—Debt issuance costs at December 31, 2016 consists of underwriting discounts and offering-related costs incurred by the Company in connection with the closing of the 2021 Convertible Notes and are included as a direct deduction from the carrying amount of the 2021 Convertible Notes on the Company's consolidated balance sheet. The Company amortizes debt issuance costs to interest expense over the life of the 2021 Convertible Notes using the effective interest method. (See Note 5). Amortization of debt issuance costs was $222 for the year ended December 31, 2016.

Debt issuance costs incurred in connection with the Company's notes payable, Convertible Bridge Notes and 2020 Convertible Notes were capitalized at the inception of the notes and amortized over the term of the respective notes using the effective interest rate method. At December 31, 2015 and 2016, the Company no longer carried the notes payable, Convertible Bridge Notes or 2020 Convertible Notes on its consolidated balance sheet (see Note 5). Amortization of deferred issuance costs was $0 and $107 for the years ended December 31, 2016 and 2015, respectively, and recorded as a component of interest expense in the accompanying consolidated statements of operations.

Deferred Public Offering Costs—Deferred public offering costs, which consist primarily of direct, incremental legal, accounting, Securities and Exchange Commission and NASDAQ Global Market fees relating to the IPO and issuance of the 2020 Convertible Notes, were capitalized as a component of other assets on the balance sheet as of December 31, 2014. At December 31, 2014, the Company had $1,846 of deferred public offering costs. In the year ended December 31, 2015, the Company incurred an additional $1,620 of public offering costs and allocated (i) $2,377 of the aggregate public offering costs to the IPO and $627 to the 2020 Convertible Notes offering, which were recorded as deferred financing costs and were amortized to interest expense from the issuance of the 2020 Convertible Notes, through the conversion of the 2020 Convertible Notes in July and August 2015; and (ii) $462 to the Follow-on Offering.

Research and Development Costs—Research and development costs are charged to expense as incurred and include, but are not limited to:

- employee-related expenses including salaries, benefits, travel and stock-based compensation expense for research and development personnel;
- expenses incurred under agreements with contract research organizations that conduct clinical and preclinical studies, contract manufacturing organizations and consultants;
- costs associated with preclinical and development activities; and
- costs associated with regulatory operations.

Costs for certain development activities, such as clinical studies, are recognized based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, and information provided to the Company by its vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the patterns of costs incurred, and are reflected in the financial statements as accrued expenses, or prepaid expenses and other current assets, if the related services have not been provided.

Stock-Based Compensation —The Company measures the cost of employee services received in exchange for an award of equity instruments based on the fair value of the award on the grant date. That cost is recognized on a straight-line basis over the period during which the employee is required to provide service in exchange for the award. The fair value of options on the date of grant is calculated using the Black-Scholes option pricing model based on key assumptions such as stock price, expected volatility and expected term. The Company's estimates of these assumptions are primarily based on historical data, peer company data and judgment regarding future trends and factors. The fair value of restricted stock awards is based on the intrinsic value of such awards on the date of grant. Compensation cost for stock purchase rights under the employee stock purchase plan is measured and recognized on the date the Company becomes obligated to issue shares of our common stock and is based on the difference between the fair value of the Company's common stock and the purchase price on such date.

The Company accounts for stock options issued to non-employees in accordance with the provisions of ASC 505-50, *Equity-Based Payments to Non-employees*, which requires valuing the stock options on their grant date and remeasuring such stock options at their current fair value as they vest.

Fair Value Measurements—The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. ASC 820, *Fair Value Measurements and Disclosures* ("ASC 820"), establishes a hierarchy of inputs used when available. Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The three levels of the fair value hierarchy are described below:

Level 1—Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly.

Level 3—Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement. The fair value of the Company's financial instruments, including cash and cash equivalents, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their respective carrying values due to the short-term nature of these instruments. The Company's assets and liabilities measured at fair value on a recurring basis include its short-term investments, warrant liabilities, convertible notes redemption rights derivative and 2020 Convertible Notes derivative liability (see Note 10). There were no material liability-classified warrants, derivatives or derivative liabilities outstanding in 2016.

Derivative Financial Instruments—All derivatives are recorded as assets or liabilities at fair value, and the changes in fair value are immediately included in earnings. The Company's derivative financial instruments include bifurcated embedded derivatives that were identified within the 2020 Convertible Notes and the Convertible Bridge Notes (see Notes 5, 7 and 10). There were no material derivative financial instruments outstanding in 2016.

Income taxes—The Company uses the asset and liability method for accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the estimated future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective income tax bases. Deferred tax assets and liabilities are measured using enacted rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. A valuation allowance is recorded if it is more likely than not that a deferred tax asset will not be realized. The Company has provided a full valuation allowance on its deferred tax assets.

The Company recognizes the financial statement benefit of a tax position only after determining that the relevant tax authority would more likely than not sustain the position following an audit. For tax positions meeting the more-likely-than-not threshold, the amount recognized in the consolidated financial statements is the largest benefit that has a greater than 50 percent likelihood of being realized upon ultimate settlement with the relevant tax authority.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2016 and 2015, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statements of operations.

Net loss per share—The Company calculates net loss per share in accordance with ASC 260, *Earnings per Share*. Basic earnings (loss) per share ("EPS") is calculated by dividing the net income or loss applicable to common stockholders by the weighted average number of common shares outstanding for the period, without consideration of unissued common stock equivalents. The net loss applicable to common stockholders is determined by the reported net loss for the period and deducting dividends accrued and accretion of preferred stock. Diluted EPS is calculated by adjusting the weighted average common shares outstanding for the dilutive effect of common stock options, warrants, and convertible preferred stock and accrued but unpaid convertible preferred stock dividends. In periods where a net loss is recorded, no effect is given to potentially dilutive securities, as their effect would be anti-dilutive.

The following table sets forth the computation of basic and diluted EPS attributable to the Company's common stockholders:

	For the Years Ended December 31,	
	2016	2015
	(in thousands, except share and per share amounts)	
Numerator:		
Net loss	$ (42,854)	$ (67,982)
Accretion and dividends on convertible preferred stock	-	(131)
Net loss applicable to common stockholders	$ (42,854)	$ (68,113)
Denominator:		
Weighted average common shares outstanding—basic and diluted	26,735,175	18,311,333
Net loss per share applicable to common stockholders—basic and diluted	$ (1.60)	$ (3.72)

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated as including them would have an anti-dilutive effect:

	For the Years Ended December 31,	
	2016	2015
Shares issuable upon conversion of the 2021 Convertible Notes	6,483,791	—
Warrants for common stock	56,408	56,408
Stock options	2,675,458	1,631,677
Restricted Stock Units	470,000	—
Total	9,685,657	1,688,085

Subsequent Events—The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the financial statements to provide additional evidence relative to certain estimates or to identify matters that require additional disclosure. The Company has completed an evaluation of all subsequent events through the date the financial statements were issued (See Note 12).

Recent Accounting Pronouncements

In August 2014, the FASB issued Accounting Standards Update ("ASU") 2014-15, *Presentation of Financial Statements-Going Concern*, which provides guidance about management's responsibility to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. The new standard is effective for the Company for the annual period ending after December 15, 2016, and for annual and interim periods thereafter, with early adoption permitted. The Company adopted this standard for the year ended December 31, 2016. The adoption of this ASU did not have a material impact on the Company's consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)*, which supersedes the current leasing guidance and upon adoption, will require lessees to recognize right-of-use assets and lease liabilities on the balance sheet for all leases with terms longer than 12 months. The new standard is effective for the Company for the annual period beginning after December 15, 2018, and can be early adopted by applying a modified retrospective approach for leases existing at, and entered into after, the beginning of the earliest comparable period presented in the financial statements. The Company is currently evaluating the impact of this accounting standard update on the Company's consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, which amends ASC Topic 718, *Compensation – Stock Compensation*, and includes provisions intended to simplify various aspects related to how share-based payments are accounted for and presented in the financial statements. The new standard is effective for the Company for the annual period beginning after December 15, 2016, and for annual and interim periods thereafter, with early adoption permitted. The adoption of this guidance is not expected to have a material impact on the Company's consolidated financial statements.

3. Property and Equipment

At December 31, 2016 and 2015, the Company's property and equipment consisted of the following:

	December 31,	
	2016	2015
	(in thousands)	
Office equipment	$ 407	$ 334
Computer hardware and software	263	252
Laboratory equipment	446	43
Leasehold improvements	445	445
Total	$ 1,561	$ 1,074
Less: accumulated depreciation	(431)	(262)
Property and equipment, net	$ 1,130	$ 812

During the years ended December 31, 2016 and 2015, the Company recognized $169 and $45 of depreciation expense, respectively.

4. Accrued Expenses and Other Current Liabilities

At December 31, 2016 and 2015, the Company's accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2016	2015
	(in thousands)	
Compensation and benefits	$ 2,171	$ 999
Research and development	1,148	375
Government payable	478	450
Professional fees	311	347
Other	308	337
Total	$ 4,416	$ 2,508

5. Debt

2021 Convertible Notes

On August 5, 2016, the Company issued an aggregate of $50,000 of the 2021 Convertible Notes. On August 30, 2016, the Company issued an additional $2,000 of 2021 Convertible Notes pursuant to the exercise of the underwriters' overallotment option. The 2021 Convertible Notes have a maturity date of August 1, 2021 ("Maturity Date"), are unsecured and accrue interest at a rate of 5.75% per annum, payable semi-annually on February 1 and August 1 of each year, beginning February 1, 2017. In connection with the issuance of the 2021 Convertible Notes, the Company incurred $3,262 of debt issuance costs which were recorded as a discount on the 2021 Convertible Notes.

Each holder of a 2021 Convertible Note (the "Holder") has the option until the close of business on the second business day immediately preceding the Maturity Date to convert all, or any portion, of the 2021 Convertible Notes held by it at an initial conversion rate of 124.7505 shares of the Company's common stock per $1 principal amount of 2021 Convertible Notes (the "Conversion Rate"). The Conversion Rate is subject to adjustment from time to time upon the occurrence of certain events, including the issuance of stock dividends and payment of cash dividends. In addition, in certain circumstances, the Conversion Rate will be increased in respect of a Holder's conversion of 2021 Convertible Notes in connection with the occurrence of one or more corporate events specified in the indenture (as supplemented, the "Indenture") governing the 2021 Convertible Notes (each such specified corporate event, a "Make-Whole Fundamental Change") that occurs prior to the Maturity Date (a "Make-Whole Fundamental Change Conversion") or in respect of a Holder's voluntary conversion of 2021 Convertible Notes other than in connection with a Make-Whole Fundamental Change (a "Voluntary Conversion"). In connection with a Make-Whole Fundamental Change Conversion or a Voluntary Conversion, the Company will increase the Conversion Rate for the 2021 Convertible Notes surrendered for conversion by a number of additional shares of the Company's common stock set forth in the Additional Shares Make-Whole Table in the Indenture, based on the applicable Stock Price (as defined in the Indenture) and Effective Date (as defined in the Indenture) for such conversion. The additional shares potentially issuable in connection with a Make-Whole Fundamental Change Conversion or a Voluntary Conversion range from 0 to 24.95 per $1 principal amount of 2021 Convertible Notes, subject to adjustment. If the Stock Price applicable to any conversion is greater than $40.00 per share, the Conversion Rate will not be increased. If the Stock Price applicable to any conversion is less than $6.68 per share, the Conversion Rate in connection with a Make-Whole Fundamental Change Conversion will not be increased but it will be increased by 24.95 shares in connection with a Voluntary Conversion. Upon conversion, Holders of the 2021 Convertible Notes will receive shares of the Company's common stock and cash in lieu of fractional shares.

Upon the occurrence of a Fundamental Change, the occurrence of certain change of control transactions or delisting events (as defined in the Indenture), each Holder may require the Company to repurchase for cash all or any portion of the 2021 Convertible Notes held by such Holder at a repurchase price equal to 100% of the principal amount thereof, plus accrued and unpaid interest thereon.

The Company, at its option, may redeem for cash all or any portion of the 2021 Convertible Notes if the last reported sale price of a share of the Company's common stock is equal to or greater than 200% of the conversion price for the 2021 Convertible Notes then in effect for at least 20 trading days (whether or not consecutive) during any 30 consecutive trading day period (including the last trading day of such period) ending within the five trading days immediately preceding the date on which the Company provides notice of redemption, at a redemption price equal to 100% of the principal amount of the 2021 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date.

If an Event of Default (as defined in the Indenture), other than certain events of bankruptcy, insolvency or reorganization involving the Company, occurs and is continuing, the trustee under the Indenture (the "Trustee") or the Holders of at least 25% in principal amount of the outstanding 2021 Convertible Notes may declare 100% of the principal of and accrued and unpaid interest, if any, on all of the 2021 Convertible Notes to be due and payable immediately. Upon the occurrence of an Event of Default relating to bankruptcy, insolvency or reorganization involving the Company, 100% of the principal of and accrued and unpaid interest, if any, on all of the 2021 Convertible Notes would become due and payable automatically.

Notwithstanding the foregoing, the Indenture provides that, to the extent the Company elects, the sole remedy for an Event of Default relating to certain failures by the Company to comply with certain reporting covenants in the Indenture, will (i) for the first 90 days after the occurrence of such an Event of Default, consist exclusively of the right to receive additional interest on the 2021 Convertible Notes at a rate equal to 0.25% per annum of the principal amount of the 2021 Convertible Notes outstanding for each day during such 90-day period on which such an Event of Default is continuing and (ii) for the period from, and including, the 91st day after the occurrence of such an Event of Default to, and including, the 180th day after the occurrence of such an Event of Default, consist exclusively of the right to receive additional interest on the 2021 Convertible Notes at a rate equal to 0.50% per annum of the principal amount of the 2021 Convertible Notes outstanding for each day during such additional 90-day period on which such an Event of Default is continuing (such additional interest, "Additional Interest"). After 180 days, if such Event of Default is not cured or waived, the 2021 Convertible Notes would be subject to acceleration in accordance with the Indenture.

The 2021 Convertible Notes are considered a hybrid financial instrument consisting of a fixed interest rate "host" and various embedded features that required evaluation as potential embedded derivatives under FASB ASC 815, *Derivatives and Hedging* ("ASC 815"). Based on the nature of the host instrument and the embedded features, management concluded that none of the conversion, put and redemption features required bifurcation and separate accounting from the host instrument. The Company determined that the Additional Interest was an embedded derivative that contains non-credit related events of default. As a result, the Additional Interest feature required bifurcation and separate accounting under ASC 815. Based on the amount of Additional Interest that would be owed and the likelihood of occurrence, the Company estimated the fair value of the Additional Interest feature to be insignificant upon issuance and as of December 31, 2016.

The issuance costs which were recorded as a discount on the debt are being amortized to interest expense over the life of the 2021 Convertible Notes using the effective interest method. As of December 31, 2016, the stated interest rate, was 5.75%, and the effective interest rate was 7.3%. Interest expense related to the 2021 Convertible Notes for the year ended December 31, 2016, was $1,418, including $222 related to amortization of the debt discount.

The table below summarizes the carrying value of the 2021 Convertible Notes as of December 31, 2016:

	December 31, 2016 (in thousands)
Gross proceeds	$ 52,000
Initial value of issuance costs recorded as debt discount	(3,262)
Amortization of debt discount	222
Carrying value	$ 48,960

2020 Convertible Notes

On February 23, 2015, the Company issued an aggregate of $20,000 of the 2020 Convertible Notes pursuant to its IPO. On March 24, 2015, the Company issued an additional $1,000 of 2020 Convertible Notes pursuant to the exercise of the underwriters' overallotment option. The 2020 Convertible Notes had a maturity date of February 15, 2020, were unsecured and accrued interest at a rate of 5.0% per annum, payable semi-annually on February 15 and August 15 of each year. In connection with the issuance of the 2020 Convertible Notes, the Company incurred $2,097 of financing costs which were recorded in other assets on the balance sheet.

Each holder of a 2020 Convertible Note, had the option to convert all or any portion of such note at an initial conversion rate of 158.7302 shares of the Company's common stock per $1 principal amount of 2020 Convertible Notes. The conversion rate was subject to adjustment from time to time upon the occurrence of certain events, including the issuance of stock dividends and payment of cash dividends. For any conversion that occurred on or after July 23, 2015, the Company would, in addition to the other consideration payable, make an interest make-whole payment to such converting holder equal to the sum of the present values of the scheduled payments of interest that would have been made on the 2020 Convertible Notes to be converted had such notes remained outstanding from the date of the conversion through the earlier of (i) the date that is three years after the conversion date and (ii) the maturity date, if the 2020 Convertible Notes had not been so converted or otherwise repurchased. Present values for the interest make-whole payment would be calculated using a discount rate equal to 2%. The Company could satisfy its obligation to pay any interest make-whole payment, at its election, in cash, shares of common stock or a combination thereof.

The 2020 Convertible Notes were convertible, at the holder's option, upon a fundamental change, as defined in the indenture. If a holder elected to convert its notes upon a fundamental change, the Company would increase the conversion rate for the 2020 convertible notes so surrendered for conversion by a number of additional shares of common stock by which the conversion rate would have increased per $1 principal amount of notes for each stock price and make-whole fundamental change effective date as set forth in the indenture. The additional shares ranged from 7.9364 to 0.

Upon a fundamental change, each holder would have the right to require the Company to repurchase for cash all of such holder's notes, or any portion thereof that is equal to $1 or an integral multiple of $1. The repurchase price of the 2020 Convertible Notes would equal 100% of the principal amount thereof, plus accrued and unpaid interest thereon. However, if the repurchase occurred after a regular record date for an interest payment, but before the distribution date of that interest payment, the holder would receive the regular interest payment and the repurchase price would equal 100% of the principal amount of the 2020 Convertible Notes to be repurchased.

The 2020 Convertible Notes were redeemable at the holder's option upon an event of default. If an event of default (other than certain events of bankruptcy, insolvency or reorganization involving the Company) occurred and was continuing, the trustee by notice to the Company, or the holders of at least 25% in principal amount of the outstanding notes by written notice to the Company and the trustee, could declare 100% of the principal and accrued and unpaid interest, if any, on all of the 2020 Convertible Notes to be due and payable immediately. Upon the occurrence of certain events of default relating to bankruptcy, insolvency or reorganization involving the Company, 100% of the principal and accrued and unpaid interest, if any, on all of the 2020 Convertible Notes would become due and payable automatically.

The indenture provided that, to the extent the Company elected and for up to 180 days, the sole remedy for an event of default relating to certain failures by the Company to comply with certain reporting covenants in the indenture, consisted exclusively of the right to receive additional interest on the 2020 Convertible Notes. The additional interest consisted of interest at an additional rate of 0.25% per annum for the first 90 days after the event of default. For the 91st to 180th day after the event of default, the additional interest would consist of interest at an additional rate of 0.50% per annum. After 180 days, if the event of default was not cured or waived, the 2020 Convertible Notes were subject to acceleration as provided in Section 6.02 of the indenture.

The Company determined that the conversion option, interest make-whole payments and the additional interest were embedded derivatives that required bifurcation and separate accounting under FASB ASC 815. Based on the characteristics of the (i) conversion option including make-whole provision, (ii) the additional interest, and (iii) the 2020 Convertible Notes, the Company estimated the fair value of the conversion option including the interest make-whole provision and the additional interest using the "with" and "without" method. Using this methodology, the Company first valued the 2020 Convertible Notes with the conversion option including make-whole provision but excluding the additional interest (the "with" scenario) and subsequently valued the 2020 Convertible Notes without the conversion option including make-whole provision and excluding the additional interest (the "without" scenario). The difference between the fair values of the 2020 Convertible Notes in the "with" and "without" scenarios was the concluded fair value of the conversion option including make-whole provision as of the measurement date. The Company developed an estimate of fair value for the 2020 Convertible Notes excluding the additional interest using a binomial lattice model. The Company modeled the decision to convert or hold by considering the maximum of the conversion or hold value at every node of the lattice in which the 2020 Convertible Notes were convertible and choosing the action that would maximize the return to the 2020 Convertible Notes' holders. The significant assumptions used in the binomial model were: the market yield and the expected volatility.

The Company estimated the fair value of the additional interest using an income approach, specifically, the risk-neutral debt valuation method that is used to derive the value of a debt instrument using the expected cash flows and the risk-free rate. The significant assumptions used in estimating the expected cash flows were: the market yield used to determine the risk-neutral probability of default and the expected recovery rate upon default.

The Company recorded $11,850 as the fair value of the combined embedded derivative liability on February 23, 2015, with a corresponding amount recorded as a discount to the 2020 Convertible Notes, related to the initial issuance of the 2020 Convertible Notes. The Company recorded approximately $573 of additional derivative liability and discount to the 2020 Convertible Notes as the fair value of the combined embedded derivative on March 24, 2015, upon the issuance of additional 2020 Convertible Notes for the exercise of the underwriters' overallotment option. The deferred financing costs and the debt discount were recorded in other assets and were being amortized to interest expense over the life of the 2020 Convertible Notes using the effective interest method. Changes in the fair value of the combined embedded derivative liability were recorded in earnings in the period in which the changes occurred.

In July and August 2015, holders of all $21,000 principal amount of the 2020 Convertible Notes elected to convert the principal into 3,333,319 shares of common stock in accordance with the terms of the 2020 Convertible Notes. In addition, the interest make-whole payment was settled with shares of common stock, at the election of the Company, resulting in the issuance of 530,072 additional shares of common stock. As of the conversion dates, the fair value of the combined embedded derivative liability was determined to be $55,216. The change in the estimated fair value of the combined embedded derivative liability from the recognition

dates to the conversion dates and for the year ended December 31, 2015, was $42,793. In addition, the Company recorded a charge of $3,716 in the year ended December 31, 2015, related to extinguishment of the 2020 Convertible Notes. As of December 31, 2015, all $21,000 of the 2020 Convertible Notes were extinguished.

Interest expense related to the 2020 Convertible Notes for the year ended December 31, 2015, was $963, including $74 related to amortization of the issuance costs and $440 related to amortization of the debt discount.

Convertible Bridge Notes

In December 2014, the Company sold an aggregate of $2,000 of subordinated convertible promissory notes to existing stockholders (the "Convertible Bridge Notes"). The Convertible Bridge Notes were scheduled to mature on June 30, 2015 and accrued interest at the rate of 8% per annum and were subordinate to all other senior indebtedness of the Company. Upon the closing of an initial public offering of common stock of at least $40,000 in gross proceeds, all outstanding principal and accrued interest thereon would automatically convert into common stock at the initial public offering price.

Pursuant to the IPO in February 2015, the Convertible Bridge Notes were converted into 337,932 shares of common stock based upon the IPO common share offering price of $6.00 per share. During the year ended December 31, 2015, the Company reflected as interest expense related to the Convertible Bridge Notes (i) $23 related to the 8% coupon rate and (ii) $128 of amortization of the initial fair value of the redemption rights derivative and issuance costs. In connection with the conversion of the Convertible Bridge Notes into common stock, the Company recorded a (i) a $480 gain in change in fair value of the of the Convertible Bridge Notes redemption rights derivative from the write off of the derivative and (ii) a loss on extinguishment of debt of $360 from the acceleration of the unamortized balance of the debt discount and issuance costs.

Notes Payable

On June 28, 2013, the Company entered into two Loan and Security Agreements (the "Loan Agreements" or "Loans") with two financial entities (the "Lenders") pursuant to which the Company issued Loans for $3,500 to each lender and received proceeds of $6,915 net of costs and fees payable to the lenders. The Loans bore interest at a rate per annum of 11.0%. The Loans would mature on October 1, 2016 and required interest-only payments for the initial 12 months and thereafter required repayment of the principal balance with interest in 27 monthly installments. Also, upon full repayment or maturity of the Loans, the Lenders would be due a termination payment of 3.0% of the initial principal amount of the Loans, or $210 (the "Loan Termination Payment").

In connection with the Loan Agreements, the Company issued to the Lenders fully-vested warrants to purchase either, at the election of the warrant holder, (i) 228,906 shares of the Company's Series AA preferred stock at an exercise price of $1.529 per share, or (ii) $350 of stock in the next round stock, as defined in the Loan Agreements, at a price that is the lowest effective price per share that is offered in the next round. The warrants expire on the earlier of (i) ten years after the date of grant, or (ii) immediately prior to an acquisition transaction, as defined in the warrants. The Company determined that the warrants should initially be classified as a liability based upon the nature of the underlying Series AA preferred stock.

In connection with the Company's IPO in February 2015, the Company exercised its right to terminate the Loan Agreements by paying the $5,347 principal balance due, the $210 Loan Termination Payment, a $160 prepayment fee calculated as 3% of the principal balance due at the time of the termination, plus $23 of interest accrued from February 1, 2015 through the payoff date. The Company made a scheduled principal payment of $243 in January 2015.

For the year ended December 31, 2015, interest expense related to the Loan Agreements was $115, including $26 related to accretion of the debt discount and termination payment. Additionally, in the year ended December 31, 2015, the Company recorded a charge for loss on extinguishment of debt of $323 related to the write-off of the unamortized debt discount.

Subsequent to the Company's IPO, the warrants issued to the lenders became exercisable for 56,408 shares of common stock at $6.204 per share. The Company calculated the fair value of the warrants at the IPO date using a Black Scholes model using the following assumptions: a fair value of $6.00 per share (the IPO price of the Company's common stock), 8.4 years to maturity, 1.70% risk-free rate, and 60% volatility. The Company determined the fair value of the warrant liability at the IPO date to be $215 and recorded a gain on change in fair value of warrant liabilities of $267 in the statement of operations for the year ended December 31, 2015. The Company determined that subsequent to this change, the warrants were exercisable at a fixed price for a fixed number of shares of common stock and qualified for equity classification under the accounting guidance, and the fair value of $215 was reclassified to additional paid-in capital as of the IPO date in the year ended December 31, 2015.

6. Income Taxes

No provision for federal or state income taxes was recorded during the years ended December 31, 2016 and 2015, as the Company incurred operating losses for each of these years.

The following table reconciles the statutory rate to the effective tax rates for each of the years ended December 31, 2016 and 2015:

	For the Years Ended December 31,	
	2016	2015
Computed at statutory rate	34.00 %	34.00 %
State income taxes	4.76	1.20
Expiration of capital loss carryforward	—	(2.13)
Tax credits	3.38	0.73
Other	(1.74)	(3.35)
Change in value of convertible notes derivatives and warrant liabilities	—	(21.16)
Valuation allowance	(40.40)	(9.29)
	— %	— %

The tax effect of significant temporary differences representing deferred tax assets and liabilities as of December 31, 2016 and 2015 is as follows:

	December 31,	
	2016	2015
	(in thousands)	
Net operating loss ("NOL") and credit carryforwards	$ 43,765	$ 35,858
Capitalized research and development costs	22,775	14,406
Other	1,963	927
Valuation allowance	(68,503)	(51,191)
	$ —	$ —

As required by ASC 740, *Income Taxes*, management of the Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets, which are comprised principally of NOL carryforwards and capitalized research and development costs. As a result of the fact that the Company has incurred tax losses from inception, management has determined that it is more likely than not that the Company will not recognize the benefits of federal and state net deferred tax assets and, as a result, a full valuation allowance has been established against its net deferred tax assets as of December 31, 2016 and 2015. The Company has offset certain deferred tax liabilities with deferred tax assets that are expected to generate offsetting deductions within the same period. During the years ended December 31, 2016 and 2015, the valuation allowance changed by $17,312 and $6,313, respectively. Realization of deferred tax assets is dependent upon the generation of future taxable income.

As of December 31, 2016, the Company had federal NOL carryforwards for income tax purposes of $105,336 that expire at various dates through 2036, and state NOL carryforwards of $62,653 that expire at various dates through 2036, available to reduce future federal and state income taxes, if any. As of December 31, 2016, the Company had federal research and development tax credits of $4,654, and state research and development tax credits of $717. If substantial changes in the Company's ownership should occur, as defined in Section 382 of the Internal Revenue Code of 1986, as amended, (the "Code"), there could be annual limitations on the amount of loss carryforwards which can be realized in future periods. The Company has determined that it has experienced prior ownership changes occurring in 2005, 2007 and 2015. The pre-change NOLs, although subject to an annual limitation, can be utilized in future years as well as any post change NOLs, provided that sufficient income is generated and no future ownership changes occur that may limit the Company's NOLs.

As of December 31, 2016 and 2015, the Company's total unrecognized tax benefits totaled $488 and $333, respectively, which if recognized would affect the effective tax rate prior to the adjustment for the Company's valuation allowance. The Company files income tax returns in the U.S. federal and Massachusetts tax jurisdictions. Starting in tax year 2016, the Company will file tax returns in the New Jersey tax jurisdiction. Tax years 2013 through 2016 remain open to examination by the tax jurisdictions in which the Company is subject to tax. Since the Company is in a loss carryforward position, the Internal Revenue Service ("IRS") and state taxing authorities are permitted to audit the earlier tax years and propose adjustments up to the amount of the NOLs generated. The Company is not currently under examination by the IRS or any other jurisdiction for any tax years.

The change in unrecognized tax benefits for each of the years ended December 31, 2016 and 2015 is as follows:

	For the Years Ended December 31,	
	2016	2015
	(in thousands)	
Balance at January 1,	$ 333	$ 284
Additions for prior year tax positions	6	—
Additions for current year tax positions	149	49
	$ 488	$ 333

The Company does not expect significant changes in its unrecognized tax benefits over the next twelve months.

7. Equity

Authorized Shares

As of December 31, 2016, the Company's authorized capital stock consisted of 120,000,000 shares of common stock, par value $0.01 per share, and 5,000,000 shares of undesignated preferred stock, par value $0.001 per share.

Reverse Stock Splits

In November 2014, the board of directors and the stockholders of the Company approved a 1-for-3.39 reverse stock split of the Company's outstanding common stock and in January 2015, the board of directors and the stockholders of the Company approved a 1-for-1.197 reverse stock split of the Company's outstanding common stock. Shares of common stock underlying outstanding stock options were proportionally reduced and the respective exercise prices were proportionally increased in accordance with the terms of the option agreements. The Company's historical share and per share information has been retroactively adjusted in the financial statements presented to give effect to these reverse stock splits, including reclassifying an amount equal to the reduction in par value to additional paid-in capital.

Common Stock

All preferences, voting powers, relative, participating, optional, or other specific rights and privileges, limitations, or restrictions of the common stock are expressly subject to those that may be fixed with respect to any shares of preferred stock. Common stockholders are entitled to one vote per share, and to receive dividends, when and if declared by the Board. There were 26,986,318 and 26,423,394 shares of common stock outstanding at December 31, 2016 and 2015, respectively.

Preferred Stock

The Company has evaluated the tranched nature of its Preferred Stock offerings described below, its investor registration rights, as well as the rights, preferences and privileges of each series of Preferred Stock and concluded that there were no freestanding derivative instruments or any embedded derivatives requiring bifurcation. Additionally, the Company assessed the conversion terms associated with its Preferred Stock and concluded that there were no beneficial conversion features. As of December 31, 2016 and 2015, there were no shares of preferred stock issued and outstanding.

Series AA Redeemable Convertible Preferred Stock

In connection with the sale of Series AA preferred stock in 2013, the Company issued warrants to purchase 852,230 shares of Series AA preferred stock at a price of $0.01 per share, with an expiration date on the earliest of (i) July 11, 2023, (ii) the closing of the Company's IPO, or (iii) the closing of a sale event, as defined in the warrant. The Company allocated $1,585 of the proceeds received to the warrants issued, representing the grant date fair value of the warrants, and accounts for these warrants as liabilities. The Company recognized any change in the fair value of the warrant liabilities each reporting period in the consolidated statements of operations (Note 10). These warrants were exercised in full during the year ended December 31, 2014 for total proceeds of $8 which was recorded as Series AA preferred carrying value. The aggregate $2,250 fair value of the warrants as of the date of each exercise was reclassified partially to Series AA preferred stock carrying value and the remainder to accumulated paid-in capital.

Due to the optional redemption feature of the Series AA preferred stock, the Company classified the Series AA preferred stock as temporary equity in the mezzanine section of the balance sheet and accreted the value to the redemption amount. The carrying amount of the Series AA preferred stock at December 31, 2014 was $46,253, including $9,976 of accrued but unpaid and undeclared dividends. All shares of Series AA preferred stock converted to shares of common stock upon the IPO in February 2015. Pursuant to

these conversions, the $46,384 carrying value of the Series AA preferred stock at the time of the IPO was reclassified as $75 to common stock par value and $46,309 additional paid-in capital.

Series X Redeemable Convertible Preferred Stock

In June 2010, the Company sold 2,451,184 shares of Series X redeemable convertible preferred stock ("Series X preferred stock") to employees and consultants to the Company at a purchase price of $0.001 per share, subject to stock purchase and restriction agreements, which included repurchase rights by the Company.

Two employees that purchased Series X preferred stock were terminated by the Company in May 2013. Upon termination, the Company repurchased an aggregate of 558,864 shares of Series X preferred stock and modified the vesting terms on the remaining 558,862 shares of Series X preferred stock held by these employees such that the Company's repurchase rights would expire upon consummation of an IPO of its common stock occurring prior to June 30, 2015. The Company estimated the fair value of the modified award at the modification date to be $950 and recognized this amount as stock-based compensation expense in 2015 as a result of the Company's February 2015 IPO.

The following table is a rollforward of unvested Series X preferred stock shares:

Unvested—December 31, 2014	558,862
Vested	(558,862)
Repurchased	—
Unvested—December 31, 2015	—

Due to the redemption feature of the Series X preferred stock, the Company classified the Series X preferred stock as temporary equity in the mezzanine section of the balance sheet at December 31, 2014. Pursuant to the IPO, all Series X preferred stock became vested and converted into common stock. Pursuant to these conversions, the $548 carrying value of the Series X preferred stock at the time of the IPO was reclassified as $5 to common stock par value and $543 additional paid-in capital.

8. Stock Plans

The Company has granted common stock options pursuant to the 2004 and 2014 Plans (as defined below) at an exercise price that is not less than the fair market value of the Company's stock as determined by the board of directors, with input from management. Prior to the Company's IPO, the board of directors had determined the estimated fair value of the Company's common stock on the date of grant based on a number of objective and subjective factors, including external market conditions, rights and preferences of securities senior to the common stock at the time of each grant, the likelihood of achieving a liquidity event such as an IPO or the sale of the Company, and third party valuations. For stock option grants prior to the IPO, the computation of expected volatility was based on the historical volatilities of peer companies. The peer companies include organizations that are in the same industry, with similar size and stage of growth. The Company estimates that the expected life of the options granted using the simplified method allowable under Staff Accounting Bulletin No. 107, *Share Based Payments*. The expected life is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post vesting termination behavior among its employee population. The interest rate for grants pursuant to the 2004 and 2014 Plans are based on the U.S. treasury bills rate for U.S. treasury bills with terms commensurate with the expected term of the option grants on the grant date of the option.

2004 Stock Option and Incentive Plan

In July 2004, the Company's board of directors adopted the 2004 Stock Option and Incentive Plan (the "2004 Plan") for the issuance of incentive stock options, restricted stock, and other equity awards, all for common stock, as determined by the board of directors to employees, officers, directors, consultants, and advisors of the Company and its subsidiaries. Only stock options were granted under the 2004 Plan. The 2004 Plan expired in February 2014 but remains effective for all outstanding options.

The following table summarizes the option activity for each of the years ended December 31, 2016 and 2015 under the 2004 Plan:

	Number of Shares	Weighted-Average Exercise Price Per Share	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2014	10,958	$ 40.58	
Exercised	—	$ —	
Expired	(41)	$ 40.58	
Outstanding as of December 31, 2015	10,917	$ 40.58	
Exercised	—	$ —	
Expired	—	$ —	
Cancelled	(291)	$ 40.58	
Outstanding as of December 31, 2016	10,626	$ 40.58	$ —
Vested and exercisable as of December 31, 2016	10,626	$ 40.58	$ —
Weighted-average years remaining on contractual life	1.25		
Unrecognized compensation cost related to non-vested stock options	$ —		

The Company recorded no stock compensation expense in the years ended December 31, 2016 and 2015 relating to stock options granted pursuant to the 2004 Plan. At December 31, 2016, all 2004 Plan options were fully vested and there was no unrecognized stock-based compensation expense relating to stock options granted pursuant to the 2004 Plan. Options outstanding as of December 31, 2016 had no intrinsic value, as the option price exceeded the fair value of the underlying shares.

2014 Stock Option and Incentive Plan

In August 2014, the Company's board of directors adopted the 2014 Stock Option and Incentive Plan (the "2014 Plan") for the issuance of incentive and non-qualified stock options, restricted stock, and other equity awards, all for common stock, as determined by the board of directors to employees, officers, directors, consultants, and advisors of the Company and its subsidiaries. Pursuant to the provisions of the 2014 Plan and approval by the board of directors, on January 1, 2017 an additional 1,079,453 shares were added to the 2014 Plan representing 4% of total common shares issued and outstanding at December 31, 2016. There were 3,034 shares available for issuance under the 2014 Plan as of December 31, 2016. The 2014 Plan expires in August 2024.

For the year ended December 31, 2016, the Company recorded aggregate stock-based compensation expense of $2,843 for stock options under the 2014 Plan: $1,521 in general and administrative expense and $1,322 in research and development expense. For the year ended December 31, 2015, the Company recorded aggregate stock-based compensation expense of $1,389 for stock options under the 2014 Plan: $795 in general and administrative expense and $594 in research and development expense.

During the year ended December 31, 2016, the board of directors granted a total of 1,156,500 ten-year term stock options to employees and directors of the Company. The fair value of each stock option granted was estimated on the grant date using a Black-Scholes stock option pricing model based on the following assumptions: an expected term of 5.31 to 6.08 years; expected stock price volatility of 76.9% to 82.4%, a risk free rate of 1.20% to 2.08%, and a dividend yield of 0%. The Company will recognize $5,950 (net of any forfeitures) of stock-based compensation expense for these stock options on a straight-line basis commencing upon the grant dates through the final vesting dates.

During 2015, the Board of Directors granted a total of 730,500 ten-year term stock options to employees and directors of the Company. The fair value of each stock option granted was estimated on the grant date using a Black-Scholes stock option pricing model based on the following assumptions: an expected term of 5.31 to 6.08 years; expected stock price volatility of 80.9% to 101.1%, a risk free rate of 1.55% to 1.85%, and a dividend yield of 0%. The Company will recognize $3,209 (net of any forfeitures) of stock-based compensation expense for these stock options on a straight-line basis commencing upon the grant dates through the final vesting dates.

On August 28, 2014, the Board of Directors granted 840,975, ten-year term, stock options to officers of the Company at an exercise price of $4.342 per share, the fair market value of the common stock as determined by the Board of Directors, on the condition that the options would be of no further force and effect if the Company did not consummate an IPO prior to the one-year anniversary of the grant date (the "IPO Condition"). The IPO Condition was met upon the Company's February 2015 IPO. These stock options vested 25% on the one-year anniversary of the grant date and the remaining 75% will vest in equal monthly installments over the following 36 months.

The fair value of the stock options granted during 2014 was estimated on the grant date using a Black-Scholes stock option pricing model based on the following assumptions: an expected term of 5 to 6.25 years; expected stock price volatility of 83.3% to 92.5%; a risk free rate of 1.63% to 1.84%; and a dividend yield of 0%. The Company is recognizing $2,798 of stock-based compensation expense for these stock options on a straight-line basis commencing upon the grant date in August 2014 through the final vesting date in August 2018. As a result of the resolution of the IPO Condition, the year ended December 31, 2015 reflects stock compensation expense calculated from the grant date in August 2014 through December 31, 2015.

The following table summarizes the option activity for each of the years ended December 31, 2016 and 2015 under the 2014 Plan:

	Number of Shares	Weighted-Average Exercise Price Per Share	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2014	900,117	$ 4.34	
Granted	730,500	$ 5.69	
Exercised	(9,857)	$ 4.34	
Cancelled	—	$ —	
Outstanding as of December 31, 2015	1,620,760	$ 4.95	
Granted	1,156,500	$ 7.77	
Exercised	(84,428)	$ 4.71	
Cancelled	(28,000)	$ 6.79	
Outstanding as of December 31, 2016	2,664,832	$ 6.16	$ 2,064
Vested and exercisable as of December 31, 2016	820,884	$ 4.97	$ 930
Weighted-average years remaining on contractual life	8.59		
Unrecognized compensation cost related to non-vested stock options	$ 7,692		

The weighted-average fair value of all stock options granted for the years ending December 31, 2016 and 2015 was $5.23 and $4.39, respectively. Intrinsic value at December 31, 2016 and 2015 is based on the closing price of the Company's common stock of $6.10 and $11.33 per share, respectively. As of December 31, 2016, all options granted are expected to vest.

In 2016, 30,118 shares of the 84,428 total options exercised were surrendered to the Company pursuant to a net exercise right.

In December 2016, the board granted to certain executive officers an aggregate of 470,000 Restricted Stock Units ("RSU's") pursuant to the 2014 Plan. Each restricted stock unit represents a contingent right to receive one share of Company common stock. Vesting for these RSU's was based equally on the achievement of two performance-based conditions, subject to continued service through such achievement dates. The intrinsic fair value of these RSU's as of the date of grant was $3,055 and no stock-based compensation expense was recorded in 2016 as the Company determined that the vesting conditions were not probable of occurring. As of December 31, 2016, there were 470,000 RSU's outstanding and an aggregate of 3,134,832 RSU's and stock options for shares of Company common stock pursuant to the 2014 Plan. In January 2017, these RSU's were modified such that instead of vesting based on the achievement of certain performance-based conditions, they will vest in equal annual installments over four years from the December 2016 date of grant, subject to continued service through such dates.

In January 2017, an additional 916,000 RSU's were granted to employees of the Company. These RSU's will vest at various times over the four years following the date of grant.

Employee Stock Purchase Plan

In November 2014, the Company's board of directors adopted and the stockholders approved the 2014 Employee Stock Purchase Plan (the "ESPP"). The ESPP provides that the number of shares reserved and available for issuance under the ESPP shall be cumulatively increased each January 1, beginning on January 1, 2016, by the lesser of (i) 600,000 shares of common stock or (ii) the number of shares necessary to set the number of shares of Common Stock under the Plan at 1% percent of the outstanding number of shares as of January 1 of the applicable year. However, the board of directors reserves the right to determine that there will be no increase for any year or that any increase will be for a lesser number of shares. As of January 1, 2017, 31,555 shares were added to the ESPP. As of December 31, 2016, there were 238,308 shares available for issuance under the ESPP.

All employees who are whose customary employment is for more than 20 hours a week are eligible to participate in the ESPP. Any employee who owns 5% or more of the voting power or value of the Company's shares of common stock is not eligible to

purchase shares under the ESPP. Each employee who is a participant in the ESPP may purchase shares by authorizing payroll deductions of up to 10% of his or her base compensation during an offering period. Unless the participating employee has previously withdrawn from the offering, his or her accumulated payroll deductions will be used to purchase shares of common stock on the last business day of the offering period at a price equal to 85% of the fair market value of the ordinary shares on the first business day or the last business day of the offering period, whichever is lower, provided that no more than 5,000 shares of common stock may be purchased by any one employee during each offering period. Under applicable tax rules, an employee may purchase no more than $25,000 worth of stock, valued at the start of the purchase period, under the ESPP in any calendar year.

In 2015, $63 was withheld and used to purchase 13,143 shares of common stock and the Company recorded $41 of stock-based compensation expense pursuant to the ESPP. In 2016, $155 was withheld and used to purchase 25,925 shares of common stock and the Company recorded $66 of stock-based compensation expense pursuant to the ESPP.

9. Commitments and Contingencies

Operating Leases

In May 2015, the Company entered into a lease agreement (the "Office Lease") for its headquarters in Lexington, Massachusetts. The Company occupied this space in September 2015, at which time its rental obligations commenced. The Company recorded $445 as leasehold improvements for costs incurred to build out the space, and is amortizing those costs to facilities expense over the term of the lease. Rent expense is recognized on a straight-line basis at the average monthly rent over the term of the lease. Deferred rent is included in other current and long-term liabilities on the Company's consolidated balance sheets.

In February 2016, the Company signed an amendment to the Office Lease, whereby it agreed to rent additional space (the "Lease Amendment"). The Company occupied the additional space on July 1, 2016. The terms of the Lease Amendment follow the terms of the Office Lease. The lease term is 90 months and the Company has the right to extend the term for one period of five years. Annual lease rates vary from $25 per square foot in the first year of the lease to $30.50 per square foot in the last year of the lease.

Rent expense was $275 and $143 for the years ended December 31, 2016 and 2015, respectively. As of December 31, 2016, the remaining aggregate annual commitments pursuant to the Office Lease and the Lease Amendment are as follows:

Year	(in thousands)
2017	$ 402
2018	411
2019	421
2020	429
2021	439
Thereafter	520
Total	$ 2,622

Termination of Chief Scientific Officer

In October 2016, the Company entered into a Transition Agreement with its former Chief Scientific Officer, William K. McVicar, Ph.D. (the "Transition Agreement"). Pursuant to the terms of the Transition Agreement, Dr. McVicar will remain an employee of the Company as a Senior Advisor for a six-month period ending April 4, 2017 (the "Transition Period") and for twelve months thereafter will receive his salary and medical benefits at the same rate in effect as of the date of the Transition Agreement. The Company recorded a charge in research and development expense of approximately $0.9 million in 2016 related to the Transition Agreement, including approximately $0.2 million related to stock options expected to vest during the Transition Period.

Indemnification Arrangements

As permitted under Delaware law, the Company's bylaws provide that the Company will indemnify any director, officer, employee or agent of the Company or anyone serving in these capacities. The maximum potential amount of future payments the Company could be required to pay is unlimited. The Company has insurance that reduces its monetary exposure and would enable it to recover a portion of any future amounts paid. As a result, the Company believes that the estimated fair value of these indemnification commitments is minimal.

Throughout the normal course of business, the Company has agreements with vendors that provide goods and services required by the Company to run its business. In some instances, vendor agreements include language that requires the Company to indemnify the vendor from certain damages caused by the Company's use of the vendor's goods and/or services. The Company has insurance that would allow it to recover a portion of any future amounts that could arise from these indemnifications. As a result, the Company believes that the estimated fair value of these indemnification commitments is minimal.

10. Fair Value of Financial Measurements

Items measured at fair value on a recurring basis include short term investments, derivative instruments and warrant liabilities.

The following table sets forth the Company's financial instruments that were measured at fair value on a recurring basis by level within the fair value hierarchy:

	Fair Value Measurements at December 31, 2016			
	Total	Level 1	Level 2	Level 3
	(in thousands)			
Assets:				
Money market mutual funds (included in cash and cash equivalents)	$ 20,698	$ 20,698	$ —	$ —
Certificates of deposit	$ 22,046	$ —	$ 22,046	$ —
Agency bonds	5,913	—	5,913	—
United States Treasury securities	68,716	68,716	—	—
Short-term investments	$ 96,675	$ 68,716	$ 27,959	$ —

	Fair Value Measurements at December 31, 2015			
	Total	Level 1	Level 2	Level 3
	(in thousands)			
Assets:				
Certificates of deposit	$ 16,160	$ —	$ 16,160	$ —
Agency bonds	10,031	—	10,031	—
United States Treasury securities	5,047	5,047	—	—
Short-term investments	$ 31,238	$ 5,047	$ 26,191	$ —

Money market mutual funds

The Company classifies its money market mutual funds as Level 1 assets under the fair value hierarchy as these assets have been valued using quoted market prices in active markets without any valuation adjustment.

Short-term investments

The Company classifies its United States Treasury securities as Level 1 assets under the fair value hierarchy as these assets have been valued using quoted market prices in active markets without any valuation adjustment. The Company classifies its certificates of deposit as Level 2 assets under the fair value hierarchy, as there are no quoted market prices in active markets, and its agency bonds as Level 2 assets under the fair value hierarchy, as these assets are not always valued daily using quoted market prices in active markets.

Convertible preferred stock warrant liability

As previously discussed (see Notes 5 and 7), the Company issued warrants to purchase Series AA preferred stock in connection with the 2013 Series AA preferred stock issuance, which were exercised in full in 2014, and Loan Agreements.

The following table details the assumptions used in the Black-Scholes option pricing model used to estimate the fair value of the Series AA preferred stock warrants as of February 17, 2015, the date upon which the Series AA preferred stock warrants became exercisable for common stock:

	February 17, 2015
Volatility	60%
Expected term (years)	8.4
Expected dividend yield	0.0%
Risk-free rate	1.7%

Convertible debt redemption rights derivative

The 2014 Convertible Bridge Notes redemption rights derivative required separate accounting and was valued using a single income valuation approach. Pursuant to the IPO, the Convertible Bridge Notes were converted into 337,932 shares of common stock.

2020 Convertible Notes derivative liability

The fair value methodologies related to the 2020 Convertible Notes derivative liability are discussed in Note 5.

During the periods presented, the Company did not change the manner in which it values liabilities that are measured at fair value using Level 3 inputs. The Company recognizes transfers between levels of the fair value hierarchy as of the end of the reporting period. There were no transfers within the hierarchy during any of the years presented.

The following table reflects the change in the Company's Level 3 liabilities for the year ended December 31, 2015:

	Convertible preferred stock warrant liabilities	Convertible Bridge Notes redemption rights derivative	2020 Convertible Notes derivative liability
		(in thousands)	
Balance at December 31, 2014	$ 482	$ 480	$ —
Issuance of 2020 Convertible Notes	—	—	12,423
Change in fair value	(267)	(480)	42,793
Reclassification to stockholders' equity	(215)	—	—
Conversion to common stock	—	—	(55,216)
Balance at December 31, 2015	$ —	$ —	$ —

11. Benefit Plans

Retirement Plan

The Company sponsors a 401(k) savings plan (the "Savings Plan") for all eligible U.S. employees. The Company reserves the right to modify, amend, or terminate the Savings Plan. Employees may contribute up to the maximum allowed by the IRS, while the Company contributes to the plan at the discretion of the board of directors. The Company's contributions to the plan for the years ended December 31, 2016 and 2015 were $168 and $35, respectively.

Management Incentive Plan

In August 2014, the Company adopted the Amended and Restated 2014 Management Incentive Plan (the "MIP") in which certain of our named executive officers participated. Pursuant to the MIP, upon a "change in control" (as defined in the MIP), a bonus pool will be created from the proceeds received in connection with such change in control (ranging from 7 percent to 9.75 percent of transaction proceeds, depending upon the level of transaction proceeds received in the transaction), and each participant is entitled to receive a bonus equal to a certain percentage of such bonus pool. The MIP terminates automatically upon the earliest of (i) March 31, 2015 (unless a change in control has occurred prior to such date), (ii) the closing of our IPO, (iii) the closing of a qualified financing, as defined in the MIP, and (iv) the date all amounts to be paid under the MIP following a change in control have been paid. The MIP terminated upon the closing of our IPO in February 2015.

12. Subsequent Event

On January 6, 2017, a purported stockholder of the Company filed a putative class action in the U.S. District Court for the District of Massachusetts, against the Company, David Southwell, Rudolf Baumgartner, Dale Ritter, and William McVicar, captioned *Whitehead v. Inotek Pharmaceuticals Corporation, et al*., No. 1:17-cv-10025. The complaint alleges violations of Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 and SEC Rule 10b-5 based on allegedly false and misleading statements and omissions regarding our MATrX-1 phase 3 clinical trial of trabodenoson. The lawsuit seeks among other things, unspecified compensatory damages, interest, attorneys' fees and costs, and unspecified equitable/injunctive relief. The Company intends to vigorously defend itself against this claim.

Exhibit Index

Exhibit Number	Description of Exhibit
1.1	Underwriting Agreement, dated as of August 1, 2016, between Inotek Pharmaceuticals Corporation and Cowen and Company, LLC (7)
3.1	Seventh Amended and Restated Certificate of Incorporation of Inotek Pharmaceuticals Corporation, effective as of February 23, 2015 (1)
3.2	Amended and Restated By-Laws of Inotek Pharmaceuticals Corporation, effective as of February 17, 2015 (1)
4.1	Form of Common Stock Certificate of Inotek Pharmaceuticals Corporation (1)
4.2	Third Amended and Restated Investor Rights Agreement, dated as of June 9, 2010, by and among the Registrant and each of the parties listed on Schedule A thereto (2)
4.3	Indenture between Inotek Pharmaceuticals Corporation, and Wilmington Trust, National Association, as the trustee, relating to the 5.0% Convertible Senior Notes due 2020 (3)
4.4	Base Indenture, dated as of August 5, 2016, by and between Inotek Pharmaceuticals Corporation and Wilmington Trust, National Association (8)
4.5	First Supplemental Indenture, dated as of August 5, 2016, by and between Inotek Pharmaceuticals Corporation and Wilmington Trust, National Association (8)
4.6	Form of 5.75% Convertible Senior Note due 2021 (8)
10.1	2004 Stock Option and Incentive Plan (2)
10.2	2014 Stock Option and Incentive Plan and forms of agreements thereunder, as amended (1)
10.3	Letter Agreement, dated as of July 28, 2014, by and between the Registrant and David P. Southwell (2)
10.4	Letter Agreement, dated as of May 2, 2007, by and between the Registrant and Dr. Rudolf A. Baumgartner, M.D., as amended and currently in effect (2)
10.5	Letter Agreement, dated as of August 23, 2007, by and between the Registrant and Dr. William K. McVicar, Ph.D., as amended and currently in effect (2)
10.6	Transition Agreement, dated as of October 4, 2016, by and between Inotek Pharmaceuticals Corporation and Dr. William K. McVicar, Ph.D., (9)
10.7	Letter Agreement, dated as of August 28, 2014, by and between the Registrant and Dale Ritter (2)
10.8	Inotek Pharmaceuticals Corporation 2014 Employee Stock Purchase Plan, dated as of November 18, 2014 (1)
10.9.1	Form of Indemnification Agreement, to be entered into between the Registrant and its directors (2)
10.9.2	Form of Indemnification Agreement, to be entered into between the Registrant and its officers (2)
10.10.1	Lease, dated as of May 29, 2015, by and between the Registrant and 91 Hartwell Avenue Trust, as amended and currently in effect (4)
10.10.2	First Amendment to Lease, dated as of February 24, 2016, by and between the Registrant and 91 Hartwell Avenue Trust (5)
10.11	Warrant to Purchase Shares of Series Preferred Stock dated as of June 28, 2013, by and among the Inotek Pharmaceuticals Corporation and Horizon Technology Finance Corporation (1)
10.12	Warrant to Purchase Shares of Series Preferred Stock dated as of June 28, 2013, by and among the Inotek Pharmaceuticals Corporation and Fortress Credit Co LLC (1)
10.13	Sales Agreement, dated as of April 4, 2016, by and between Inotek Pharmaceuticals Corporation and Cowen and Company, LLC (6)
1 21.1*	List of Subsidiaries
1 23.1*	Consent of RSM US LLP

Exhibit Number	Description of Exhibit
24.1*	Power of Attorney (included in the signature page)
31.1*	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1*	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document.
101.SCH	XBRL Taxonomy Extension Schema Document.
101.CAL	XBRL Taxonomy Extension Calculation Document.
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document.
101.PRE	XBRL Taxonomy Extension Presentation Link Document.

* Filed herewith.

(1) Filed as an Exhibit to the Company's annual report on Form 10-K (001-36829), filed with the SEC on March 31, 2015, as amended, and incorporated herein by reference.

(2) Filed as an Exhibit to the Company's registration statement on Form S-1 (333-199859), filed with the SEC on November 5, 2014, as amended, and incorporated herein by reference.

(3) Filed as an Exhibit to the Company's current report on Form 8-K (001-36829), filed with the SEC on February 26, 2015, and incorporated herein by reference.

(4) Filed as an Exhibit to the Company's current report on Form 8-K (001-36829), filed with the SEC on June 1, 2015, and incorporated herein by reference.

(5) Filed as an Exhibit to the Company's current report on Form 8-K (001-36829), filed with the SEC on February 26, and incorporated herein by reference.

(6) Filed as an Exhibit to the Company's registration statement on Form S-3 (333-210585), filed with the SEC on April 4, 2016, as amended, and incorporated herein by reference.

(7) Filed as an Exhibit to the Company's current report on Form 8-K (001-36829), filed with the SEC on August 3, 2016, and incorporated herein by reference.

(8) Filed as an Exhibit to the Company's current report on Form 8-K (001-36829), filed with the SEC on August 5, 2016, and incorporated herein by reference.

(9) Filed as an Exhibit to the Company's quarterly report on Form 10-Q (001-36829), filed with the SEC on November 9, 2016, as amended, and incorporated herein by reference.

Exhibit 21.1

Subsidiaries of Inotek Pharmaceuticals Corporation

	Subsidiary	Jurisdiction of Incorporation	Inotek Ownership
1.	Inotek Securities Corporation	Massachusetts	100%
2.	Inotek Ltd.	Bermuda	100%

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Forms S-8 (Nos. 333-204501 and 333-212308) and on Form S-3 (No. 333-210585) of Inotek Pharmaceuticals Corporation of our report dated March 16, 2017, relating to the consolidated financial statements of Inotek Pharmaceuticals Corporation, appearing in this Annual Report on Form 10-K of Inotek Pharmaceuticals Corporation for the year ended December 31, 2016.

/s/ RSM US LLP

Boston, Massachusetts
March 16, 2017

Exhibit 31.1

Certifications under Section 302

I, David P. Southwell, certify that:

1. I have reviewed this annual report on Form 10-K of Inotek Pharmaceuticals Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2017

/s/ David P. Southwell

David P. Southwell
President, Chief Executive Officer and Director
(Principal Executive Officer)

Exhibit 31.2

Certifications under Section 302

I, Dale Ritter, certify that:

1. I have reviewed this annual report on Form 10-K of Inotek Pharmaceuticals Corporation;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on my most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2017

/s/ Dale Ritter

Dale Ritter
Vice President–Finance
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the annual report on Form 10-K of Inotek Pharmaceuticals Corporation (the "Company") for the period ended December 31, 2016, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers hereby certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350, that their knowledge:

1) the Report which this statement accompanies fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 16, 2017

/s/ David P. Southwell
David P. Southwell
President, Chief Executive Officer and Director
(Principal Executive Officer)

Date: March 16, 2017

/s/ Dale Ritter
Dale Ritter
Vice President–Finance
(Principal Financial Officer)

The foregoing certifications are not deemed filed with the Securities and Exchange Commission for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (Exchange Act), and are not to be incorporated by reference into any filing of Inotek Pharmaceuticals Corporation under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, regardless of any general incorporation language in such filing.