AERIE PHARMACEUTICALS INC
Form 10-K
March 02, 2016
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

FORM 10-K

(Mark One)
ý ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015
or
o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
Commission File Number: 001-36152

Aerie Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware	20-3109565
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

2030 Main Street, Suite 1500
Irvine, California 92614
(949) 526-8700
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.001 par value per share	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 o No ý
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes o No ý
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 ý No o

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 during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files): Yes ý No o

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 the 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. o

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 o	Accelerated filer ý
Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

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

The aggregate market value of the voting stock held by non-affiliates of the registrant on June 30, 2015, based upon the closing price of $17.65 of the registrant's common stock as reported on the NASDAQ Global Market, was $298,090,000. Shares of the registrant's common stock held by each officer and director and each person known to the registrant to own 10% or more of the outstanding voting power of the registrant have been excluded because such persons may be deemed affiliates. This determination of affiliate status is not a determination for other purposes.

As of February 25, 2016, the registrant had 26,511,882 shares of common stock, $0.001 par value, issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement (the "Proxy Statement") for the 2016 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K. The Proxy Statement will be filed with the Securities and Exchange Commission (the "SEC") within 120 days of the registrant's fiscal year ended December 31, 2015.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). We may, in some cases, use terms such as "predicts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "would," "could," "might," "will," "should," "exploring," "pursuing" or ot convey uncertainty of future events or outcomes to identify these forward-looking statements.

Forward-looking statements appear in a number of places throughout this report and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things:

- the success, timing and cost of our ongoing and anticipated preclinical studies and clinical trials for our current and potential future product candidates, including statements regarding the timing of initiation and completion of the studies and trials;
- our expectations regarding the clinical effectiveness of our product candidates and results of our clinical trials;
- the timing of and our ability to obtain and maintain U.S. Food and Drug Administration ("FDA") or other regulatory authority approval of, or other action with respect, to our product candidates;
- our expectations related to the use of proceeds from our initial public offering ("IPO") in October 2013, the issuance and sale of the 2014 Convertible Notes (as defined herein) in September 2014 and the issuance and sale of common stock under our shelf registration statement on Form S-3 and "at-the-market" sales agreements;
- our estimates regarding anticipated capital requirements and our needs for additional financing;
- the commercial launch and potential future sales of our current or any other future product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- third-party payor reimbursement for our product candidates;
- the glaucoma patient market size and the estimated rate and degree of market adoption of our product candidates by eye-care professionals and patients;
- the timing, cost or other aspects of the commercial launch of our product candidates;
- our plans to pursue development of our product candidates for additional indications and other therapeutic opportunities;
- the potential advantages of our product candidates;
- our plans to explore possible uses of our existing proprietary compounds beyond glaucoma;
- our ability to protect our proprietary technology and enforce our intellectual property rights;
- our expectations regarding collaborations, licensing, acquisitions and strategic operations, including our ability to in-license or acquire additional ophthalmic products or product candidates; and
- our stated objective of building a major ophthalmic pharmaceutical company.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics and industry change, and depend on regulatory approvals and economic and other environmental circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. We discuss many of these risks in greater detail under the heading "Risk Factors" in Part I, Item 1A of this report and elsewhere in this report. You should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this report, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this report. In addition, even if our results of operations, financial condition and liquidity, and events in the industry in which we operate are consistent with the forward-looking statements contained in this report, they may not be predictive of results or developments in future periods.

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Any forward-looking statements that we make in this report speak only as of the date of this report. Except as required by law, we are under no duty to update or revise any of the forward-looking statements, whether as a result of new information, future events or otherwise, after the date of this report.

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PART I

ITEM 1. BUSINESS

Overview

We are a clinical-stage pharmaceutical company focused on the discovery, development and commercialization of first-in-class therapies for the treatment of patients with glaucoma and other diseases of the eye. Our strategy is to advance our product candidates, including Rhopressa™ (netarsudil ophthalmic solution) 0.02%, and Roclatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%, to regulatory approval and commercialize these products ourselves in North American markets. We plan to build a commercial team of approximately 100 sales representatives to target approximately 10,000 high prescribing eye-care professionals throughout North America. We are also directing our own clinical trials to gain regulatory approval in Europe, and are preparing to either use a contract research organization, or otherwise partner, to conduct the necessary trials to gain approval in Japan. For commercialization outside of North America, we may potentially commercialize ourselves in Europe and expect to explore partnership opportunities through collaboration and licensing arrangements in Europe and Japan. We expect to finalize our European commercialization strategy by the end of 2016. We are enhancing our longer-term commercial potential by identifying and advancing additional product candidates, including through our internal discovery efforts, research collaborations, potential in-licensing or acquisitions of additional ophthalmic products or technologies or product candidates that would complement our current product portfolio.

We completed our IPO in October 2013 which raised net proceeds of approximately $68.3 million. Since our IPO we have raised additional net proceeds of approximately $122.9 million through the sale and issuance of the 2014 Convertible Notes in September 2014, and approximately $50.5 million through at-the-market sales during 2015. Our senior leadership team has extensive experience in the ophthalmology market and has overseen the development and commercialization of several successful ophthalmic products at major pharmaceutical companies. If our products are approved and we are commercially successful, we believe Aerie could become a major ophthalmic pharmaceutical company.

Our two advanced stage product candidates are designed to lower intraocular pressure, or IOP, in patients with open-angle glaucoma and ocular hypertension. Both product candidates are taken once-daily and have shown in preclinical and clinical trials to be effective in lowering IOP, with novel mechanisms of action, or MOAs, and a positive safety profile. Glaucoma is one of the largest segments in the global ophthalmic market. In 2014, branded and generic glaucoma product sales exceeded $4.7 billion in the United States, Europe and Japan in aggregate, according to IMS. Prescription volume for glaucoma products in the United States alone exceeded 33 million in 2014 and is expected to grow, driven in large part by the aging population.

Our lead product candidate is once-daily Rhopressa™. We successfully completed our second Phase 3 registration trial for Rhopressa™, named “Rocket 2,” in September 2015, which will be the pivotal trial for a New Drug Application, or NDA, filing with the U.S. Food and Drug Administration, or FDA, that we expect to submit in the third quarter of 2016. The primary clinical efficacy endpoint was to demonstrate non-inferiority of IOP lowering of Rhopressa™ compared to timolol in a 90-day efficacy period. The final primary baseline IOP ranges for Rocket 2 were above 20 mmHg (millimeters of mercury) to below 25 mmHg. In addition to successfully achieving non-inferiority to timolol at this endpoint range, the recently reported topline 12-month safety data from Rocket 2 confirmed a positive safety profile for the drug and demonstrated a consistent IOP lowering effect throughout the 12-month period at the specified timepoint.

As background, the final primary endpoint range for Rocket 2 was updated from the original trial design, which included baseline IOPs of up to 27 mmHg. This change in endpoint range was made while Rocket 2 was in progress and prior to the database being locked, and was performed with FDA agreement. The reason for the change was the failure of our first Phase 3 registration trial for Rhopressa™, named “Rocket 1.” This 90-day efficacy trial did not meet its primary clinical efficacy endpoint of demonstrating non-inferiority of IOP lowering of Rhopressa™ compared to timolol at its primary range of above 20 mmHg to below 27 mmHg, which we reported in April 2015 (while Rocket 2 was

already underway). Rocket 1 was successful at its pre-specified secondary endpoint range of above 20 mmHg and below 24 mmHg, and it was agreed by the FDA that Rocket 1, because of its success in meeting the secondary endpoint range, could be used as supportive to Rocket 2 for the upcoming NDA filing.

We are also conducting a third Phase 3 registration trial for Rhopressa™, named “Rocket 3,” in Canada, which is a supplementary 12-month safety-only trial and is not required for NDA filing purposes. In addition, we are conducting a fourth Phase 3 registration trial for Rhopressa™, named “Rocket 4,” in the U.S., which is designed to generate the six-month safety data that will be needed for European approval purposes, and is also not required for NDA filing purposes. We expect to report the topline 90-day interim efficacy data for Rocket 4 in the fourth quarter of 2016.

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We are developing Rhopressa™ as the first of a new class of compounds that is designed to lower IOP in patients through novel MOAs. We believe that, if approved, Rhopressa™ will represent the first new MOAs for lowering IOP in patients with glaucoma in over 20 years. Based on clinical data to date, we expect that Rhopressa™, if approved, will compete with non-PGA (prostaglandin analog) products as a preferred adjunctive therapy to PGAs, due to its IOP-lowering ability at consistent levels across tested baselines with once-daily dosing relative to currently marketed non-PGA products and its potential synergistic effect with PGA products. Adjunctive therapies currently represent approximately one-half of the entire glaucoma therapy market in the United States. In addition, if approved, we believe that Rhopressa™ may also become a preferred therapy where PGAs are contraindicated, for patients who do not respond to PGAs, for patients who have lower IOPs but nevertheless present with glaucomatous damage to the optic nerve, which is commonly referred to as “low-tension” or “normal tension” glaucoma, as well as for patients who choose to avoid the cosmetic issues associated with PGA products.

Our second product candidate is once-daily Roclatan™. Roclatan™ is a fixed-dose combination of Rhopressa™ and latanoprost, which is the most commonly prescribed drug for the treatment of patients with glaucoma. We currently have one Phase 3 registration trial for Roclatan™ in process with a second about to start, after having successfully completed a Phase 2b clinical trial for patients with open-angle glaucoma and ocular hypertension in June 2014. In the the Phase 2b clinical trial, Roclatan™ achieved its primary efficacy endpoint on day 29 and statistical superiority over individual components at all timepoints. We believe Roclatan™ has the potential to provide a greater IOP-lowering effect than any currently approved glaucoma product. Therefore, we believe that Roclatan™, if approved, could compete with both PGA and non-PGA therapies and become the product of choice for patients requiring maximal IOP lowering.

The first Phase 3 registration trial for Roclatan™, named “Mercury 1,” commenced in September 2015. We expect to commence our second Phase 3 registration trial for Roclatan™ , named “Mercury 2,” in March 2016. Mercury 1 is a 12-month safety trial which includes a 90-day interim efficacy readout and Mercury 2 is a 90-day efficacy trial. Both trials are designed to demonstrate superiority of Roclatan™ to each of its components, similar to the successful Phase 2b trial. If both Mercury 1 and Mercury 2 are successful, we expect to file an NDA for Roclatan™ in the second half of 2017, approximately one year after the NDA filing for Rhopressa™.

We believe our clinical plans for both Rhopressa™ and Roclatan™ are already in place to satisfy European regulatory requirements. In addition to Rocket 1 and Rocket 2, the Rocket 4 trial is designed to provide adequate six month safety data for Rhopressa™ to meet European requirements. Based on our Rhopressa™ clinical plan, we expect to file for regulatory approval in Europe by mid-2017. While Mercury 1 and Mercury 2 will be used for European approval for Roclatan™, we also plan to initiate a third Phase 3 registration trial for Roclatan™, named “Mercury 3,” in Europe in the first half of 2017. Mercury 3 will be designed to compare Roclatan™ to a fixed dose combination product broadly marketed in Europe, which if successful should improve our commercialization prospects in that region.

Our stated objective is to build a major ophthalmic pharmaceutical company. In addition to our primary product candidates, Rhopressa™ and Roclatan™, we are also exploring the longer-term impact of Rhopressa™ on the diseased trabecular meshwork, as well as for neuroprotection, and evaluating possible uses of our existing proprietary portfolio of Rho Kinase inhibitors beyond glaucoma. In February 2015, we issued a research update on preclinical results demonstrating the potential for Rhopressa™ to have disease-modifying activity in glaucoma patients by stopping fibrosis in the trabecular meshwork, and also increasing perfusion in the trabecular outflow pathway thus increasing both drainage and the delivery of nutrients to the diseased tissue. Additionally, our preclinical small molecule, AR-13154, has shown preclinically the potential to decrease lesion size in wet age-related macular degeneration (AMD) at numerically higher levels than a current market-leading product.

We may license, acquire or develop additional product candidates and technologies to broaden our presence in ophthalmology. In August 2015 and September 2015, we entered into collaboration and license arrangements with GrayBug, Inc. and Ramot at Tel Aviv University, Ltd., respectively, neither of which represents a material financial commitment by Aerie. Our collaboration with GrayBug is focused on researching the potential use of their

biodegradable polymer technology to deliver a version of AR-13154 to the back of the eye over a sustained period of time. With Ramot, we are evaluating a Ramot preclinical anti-beta amyloid small molecule, named EG-30, for neuroprotection in glaucoma and reduction of geographic atrophy in advanced dry AMD. We continually explore and discuss potential additional opportunities for new ophthalmic products, delivery alternatives and new therapeutic areas with potential partners.

We own the worldwide rights to all indications for our current Aerie product candidates. Our intellectual property portfolio contains patents and pending patent applications related to composition of matter, pharmaceutical compositions and methods of use for our product candidates. We have patent protection for our primary product candidates, Rhopressa™ and Roclatan™ , in the United States through at least 2030.

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In March 2015, we revised our corporate structure to align with our business strategy outside of North America by establishing Aerie Pharmaceuticals Limited, a wholly-owned subsidiary organized under the laws of the Cayman Islands ("Aerie Limited"). In addition, we assigned the beneficial rights to our non-U.S. and non-Canadian intellectual property to Aerie Limited (the "IP Assignment"). As part of the IP Assignment, we and Aerie Limited entered into a research and development agreement and cost sharing agreement pursuant to which we and Aerie Limited will share the costs of the development of intellectual property. Additionally, in April 2015, we continued to prepare for foreign-based activities and established Aerie Pharmaceuticals Ireland Limited ("Aerie Ireland Limited") as a wholly-owned subsidiary of Aerie Limited to develop and commercialize the beneficial rights of the intellectual property assigned as part of the IP Assignment pursuant to a license arrangement to be entered into between Aerie Limited and Aerie Ireland Limited. We are currently evaluating the possibility of constructing an Aerie manufacturing plant in Ireland.

As indicated earlier, glaucoma is one of the largest segments in the global ophthalmic market. In 2014, branded and generic glaucoma product sales exceeded $4.7 billion in the United States, Europe and Japan in aggregate, according to IMS. Prescription volume for glaucoma products in the United States alone exceeded 33 million in 2014 and is expected to grow, driven in large part by the aging population. The PGA and non-PGA market segments each represent approximately one-half of the prescription volume in the U.S. glaucoma market, as shown in the following pie chart, which is based on IMS data.

According to the National Eye Institute, it is estimated that over 2.7 million people in the United States suffer from glaucoma, a number that is expected to reach 4.3 million by 2030. Furthermore, The Eye Diseases Prevalence Research Group has estimated that only half of the nation's glaucoma sufferers know that they have the disease. Glaucoma is a progressive and highly individualized disease, in which elevated levels of IOP are associated with damage to the optic nerve, resulting in irreversible vision loss and potentially blindness. Patients may suffer the adverse effects of glaucoma across a wide range of IOP levels, including within the "normotensive" range of 10 mmHg to 21 mmHg, which is generally accepted as the level of IOP in healthy individuals. There are multiple factors that can contribute to an individual getting glaucoma, including, but not limited to, age, family history and ethnicity. For example, there generally is a higher incidence and severity of the disease in African-American and Hispanic populations. Based on data from the Baltimore Eye Survey, approximately 80% of glaucoma patients have low to moderately elevated IOP at the time of diagnosis and approximately 60% of glaucoma patients have IOP of 21 mmHg or below at the time of diagnosis. Additionally, in Japan, the Tajimi Study found that approximately 90% of glaucoma patients had IOP of 21 mmHg or below at the time of diagnosis. In clinical trials to date, Rhopressa™ has demonstrated the ability to provide relatively consistent IOP lowering across all tested baseline IOP levels, which we believe differentiates it from currently marketed drugs that have shown reduced efficacy at lower baseline IOPs.

Glaucoma is treated by the reduction of IOP, which has been shown to slow the progression of vision loss. In a healthy eye, fluid is continuously produced and drained in order to maintain pressure equilibrium and provide nutrients to the eye tissue. The FDA recognizes sustained lowering of IOP as the primary clinical endpoint for the approval of drugs to treat patients with glaucoma and ocular hypertension. The primary drainage mechanism of the eye is the trabecular meshwork, or TM, which accounts for approximately 80% of fluid drainage in a healthy eye, while the secondary drainage mechanism, the uveoscleral pathway, is responsible for the remaining drainage. In glaucoma patients, damage to the TM results in insufficient drainage of fluid from the eye, which causes increased IOP and damage to the optic nerve. In addition to eye fluid production and drainage through the TM and uveoscleral pathway, episcleral venous pressure, or EVP, makes a significant contribution to IOP. EVP represents the pressure of the blood in the episcleral veins of the eye where the eye fluid drains into the bloodstream. Historical

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studies have shown that EVP accounts for approximately half of IOP in normotensive subjects and approximately one-third of IOP in patients with pressures of 24 to 30 mmHg. When EVP is lowered, fluid is able to flow more freely from the eye. Drugs that lower IOP without lowering EVP are most effective at high IOPs, where EVP is believed to contribute less to IOP, and are less effective at lower IOPs, where EVP is seen to account for a larger portion of IOP.

Once glaucoma develops, it is a chronic condition that requires life-long treatment. The initial treatment for glaucoma patients is typically the use of prescription eye drops. PGAs have become the most widely prescribed glaucoma drug class. The most frequently prescribed PGA is once-daily latanoprost. The most commonly prescribed non-PGA drugs belong to the beta blocker class. The most frequently prescribed beta blocker is twice-daily timolol. Other non-PGA drug classes include the alpha agonists and carbonic anhydrase inhibitors. When PGA monotherapy is insufficient to control IOP or contraindicated due to concerns about side effects, non-PGA products are used either as add-on therapy to the PGA or as an alternative monotherapy. It is estimated that up to 50% of glaucoma patients receiving PGA monotherapy require add-on therapy within two years of initial prescription of the drug, in order to maintain adequate control of IOP. It is believed that this rise in IOP after a patient is on an initial therapy results from the lack of effect of current therapies on the TM, and as a result damage to the TM progresses and the IOPs begin to rise.

Based on our preclinical studies and clinical trials to date, our product candidates represent a new class of drugs utilizing novel MOAs that are applied topically as once-daily eye drops. Currently approved drugs mainly reduce IOP by increasing fluid outflow through the eye's secondary drain with once-daily dosing or reducing fluid inflow by decreasing fluid production with multiple doses per day. Rhopressa™ lowers IOP through a triple MOA that (i) relaxes the contracted tissue of the TM to improve fluid outflow through the eye's primary drain, (ii) decreases fluid production in the eye and (iii) lowers EVP, an MOA that we believe further differentiates Rhopressa™ from currently marketed glaucoma products. Roclatan™, our quadruple-action fixed-combination product candidate, combines the triple MOA of Rhopressa™ with latanoprost, a PGA that increases fluid drainage through the uveoscleral pathway.

We believe there are significant unmet needs in the glaucoma market and that eye-care professionals are eager for new therapy choices. None of the commonly prescribed PGAs or non-PGAs target the TM, the diseased tissue responsible for elevated IOP levels in glaucoma patients and the eye's primary drain. Moreover, PGAs have side effects, contraindications and reduced efficacy in patients with low to moderately elevated IOPs relative to patients with higher IOPs. Non-PGAs are less efficacious than PGAs, have more serious and a greater number of side effects and contraindications, and require multiple daily doses. As a result, we believe there is a significant unmet need in both the PGA and non-PGA market segments, each of which represents approximately one-half of the U.S. and European glaucoma market based on prescription volumes. Despite the limitations of existing glaucoma drugs, Xalatan (latanoprost), the best-selling PGA, together with Xalacom, its fixed-combination with a beta blocker, which is not available in the United States, generated peak annual global revenues of approximately $1.7 billion prior to the introduction of their generic equivalents, and the most commonly prescribed non-PGA drugs each generated peak annual global revenues of over $400 million prior to the introduction of their generic equivalents.

We believe Rhopressa™ may be prescribed by eye-care professionals as an add-on drug of choice for patients taking PGAs, due to the MOAs of Rhopressa™ being complementary to the MOA of PGAs, and due its IOP-lowering ability, more convenient dosing and better tolerability profile compared to currently marketed non-PGA add-on products.

In addition to the expected primary use of Rhopressa™ as an adjunctive therapy, we also believe Rhopressa™ may be prescribed by eye-care professionals in the following circumstances:

- As a preferred alternative therapy for patients who do not respond to PGAs.
- As a preferred initial therapy for patients with low or normal-tension glaucoma.
- As a preferred initial therapy where PGAs are contraindicated and for patients who choose to avoid the cosmetic issues associated with PGAs, including iris color change in light-eyed patients, discoloration of tissue surrounding the eyes and eyelid droopiness and sunken eyes caused by loss of orbital fat.

In addition, based on our preclinical data to date, we believe that quadruple-action Roclatan™ would be the only glaucoma product that covers the full spectrum of currently known IOP-lowering MOAs, giving it the potential to provide a greater IOP-lowering effect than any currently approved glaucoma product. Therefore, we believe Roclatan™ could compete with both PGA and non-PGA therapies for patients requiring maximal IOP lowering, including those

with higher IOPs and those who present with significant disease progression despite currently available therapies. We currently plan to commercialize our products ourselves in North America, may commercialize ourselves in Europe and plan to explore partnership opportunities through collaboration and licensing arrangements in certain key markets outside of North

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America, including Europe and Japan, where as noted in the Tajimi study, glaucoma patients tend to have lower IOPs, in ranges where currently marketed products tend to be less effective.

Our Product Pipeline

Our primary product candidates, triple-action Rhopressa™ (netarsudil ophthalmic solution) 0.02%, and quadruple-action Roclatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%, are once-daily eye drops. The references to triple and quadruple action are supported by our preclinical studies and clinical trials to date. Rhopressa™ inhibits Rho Kinase, or ROCK, and the norepinephrine transporter, or NET, which are both novel biochemical targets for lowering IOP. By inhibiting these targets, we believe Rhopressa™ reduces IOP via three separate MOAs: (i) through ROCK inhibition, it increases fluid outflow through the TM, which accounts for approximately 80% of fluid drainage from the eye; (ii) also through ROCK inhibition, as demonstrated in a preclinical study, it reduces EVP, which represents the pressure of the blood in the episcleral veins of the eye where eye fluid drains into the bloodstream; and (iii) through NET inhibition, it reduces the production of eye fluid. Roclatan™, a single-drop fixed-dose combination of Rhopressa™ and latanoprost, lowers IOP through the same three MOAs as Rhopressa™ and, as a fourth MOA, through the ability of latanoprost to increase fluid outflow through the uveoscleral pathway, the eye's secondary drain. All of these observations represent findings from Aerie's body of preclinical and clinical work, as applicable.

We discovered and developed our product candidates internally through a rational drug design approach that coupled medicinal chemistry with high content screening of compounds in proprietary cell-based assays. We selected and formulated our product candidates for preclinical in vivo testing following a detailed characterization of over 3,000 synthesized ROCK-selective and ROCK/NET inhibitors. We continue to seek to discover and develop new compounds in our research laboratories and employ a scientific staff with expertise in medicinal chemistry, analytical chemistry, biochemistry, cell biology, pharmacology and pharmaceutical science.

The following table summarizes each of our existing product candidates, their MOAs and their development status, as well as our intellectual property rights for these product candidates.

Product Candidate and Mechanism		Phase of Development	Intellectual Property Rights
Rhopressa™	Triple-action—ROCK/NET inhibitor	Phase 3	Wholly-Owned
Roclatan™	Quadruple-action—ROCK/NET inhibitor and latanoprost, a PGA	Phase 3	Wholly-Owned

In 2015, we decided to no longer actively pursue further development of AR-13533, a second generation ROCK/NET inhibitor, merely for strategic business purposes. We have not yet submitted an IND for AR-13533 to the FDA.

Rhopressa™

Rhopressa™ is the first of a new class of glaucoma drug products that was discovered by our scientists. It is a once-daily eye drop designed to reduce IOP in patients with glaucoma or ocular hypertension. Based on our preclinical and clinical observations, it increases fluid outflow through the primary drain of the eye while also reducing eye fluid production. In addition, a preclinical study demonstrated reduction of EVP as an additional MOA of Rhopressa™, as further described below. The active ingredient in Rhopressa™, AR-13324, acts through the inhibition of both ROCK and NET.

ROCK is a protein kinase, which is an enzyme that modifies other proteins by chemically adding phosphate groups to them. Specifically, ROCK regulates actin and myosin, which are proteins that are responsible for cellular contraction. ROCK activity also promotes the production of extracellular matrix proteins. ROCK inhibitors block TM cell contraction and reduce the production of extracellular matrix, thereby improving fluid outflow and consequently decreasing IOP. In addition, we believe ROCK inhibition may also be responsible for reduction of EVP. EVP represents the pressure of the blood in the episcleral veins of the eye, where eye fluid drains into the bloodstream. When EVP is lowered, the fluid is able to flow more freely from the eye.

NET is a protein that transports norepinephrine across neuronal cell membranes. Norepinephrine is a chemical released by neurons to communicate with targeted cells. NET returns excess norepinephrine back into the neuron, which helps end the signaling between the neuron and the neuron's target cells. We believe the inhibition of NET prolongs the activation of target

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cells in the ciliary body of the eye, which reduces the production of eye fluid and thereby lowers IOP. Based on our clinical trials, we have observed that Rhopressa™ may also have a potential synergisitic effect with PGAs, whereby its IOP-lowering ability is increased when patients take a PGA as a first line therapy.

Rhopressa™ is expected to compete primarily in the adjunctive therapy market, which represents approximately one-half of the U.S. glaucoma prescription market, which totaled 33 million prescriptions in 2014 according to IMS. Currently marketed adjunctive therapies are older generation products that are generally dosed two to three times a day, have MOAs focused on fluid production reduction, often have lower efficacy levels and have systemic side effects. We believe Rhopressa™ will be able to compete with these products due to its effective IOP-lowering at relatively consistent levels across tested IOPs including the ability to lower EVP, targeting of the diseased tissue, potential synergistic effect with PGAs, convenient once-daily dosing, and favorable tolerability profile with lack of systemic side effects.

Based on the Rhopressa™ Rocket 1 and Rocket 2 Phase 3 registration trial results, Phase 2b clinical trial results, performance of Rhopressa™ in the Roclatan™ Phase 2b clinical trial and the several positive differentiating attributes of Rhopressa™, we believe Rhopressa™ has the potential to be the future drug of choice as adjunctive therapy to PGAs when additional IOP lowering is desired and as an initial therapy for PGA non-responders or for patients with low or normal-tension glaucoma and those with tolerability concerns.

Rhopressa™ Phase 3 Efficacy Results

Our Phase 3 registration trials commenced in July 2014 and are designed to use timolol as the comparator, as timolol represents the most widely used comparator in registration trials in glaucoma, and is also the most widely prescribed non-PGA drug. We anticipate a total enrollment of approximately 2,030 patients in our Phase 3 registrations trials of Rhopressa™. Phase 3 efficacy results are determined after three months of treatments and safety results are analyzed and submitted following 12 months of treatment.

In April 2015, we completed our initial Phase 3 registration trial, named “Rocket 1,” which was designed to measure efficacy over three months. Baseline IOP was measured prior to treatment. Following treatment, IOP was measured at 8 a.m., 10 a.m. and 4 p.m. at the end of week two, week four and day 90. This trial included 182 patients in the Rhopressa™ once-daily (QD) arm and 188 patients in the timolol twice-daily (BID) arm. The baseline IOPs tested in the trial ranged from above 20 to below 27 mmHg. Rhopressa™ did not achieve its primary endpoint of demonstrating non-inferiority of IOP lowering for Rhopressa™ compared to timolol for patients with IOP below 27 mmHg, but did achieve its pre-specified secondary endpoint, demonstrating non-inferiority of IOP lowering for Rhopressa™ compared to timolol for patients with IOP below 24 mmHg. We believe the lack of success at the top end of the range is attributed, at least in part, to patient non-compliance and the probability that certain patient baseline IOP levels exceeded the entry criteria of below 27 mmHg.

For the Rhopressa™ population of patients with IOP below 27 mmHg in Rocket 1, the mean difference from timolol ranged from -0.4 to +1.3 mmHg at a 95% confidence interval. For the population of patients with IOP below 26 mmHg, Rhopressa™ met the criteria for non-inferiority to timolol at all 9 time points and was numerically superior to timolol at the majority of time points. For the prespecified population of patients with IOP below 24 mmHg, Rhopressa™ met the criteria for non-inferiority to timolol at all 9 time points and was numerically superior to timolol at all 9 time points.

No drug-related serious adverse events, or SAEs, were identified during the Rocket 1 trial. The primary adverse event was conjunctival hyperemia, or eye redness, which was experienced by approximately 35% of the Rhopressa™ patients, of which approximately 80% was reported as mild. Conjunctival hyperemia was measured by biomicroscopy at 8am at the end of week two, week four and day 90. Across the population of patients on Rhopressa™, approximately 5% to 13% of subjects experienced conjunctival hemorrhage, erythema of the eyelid, blurry vision and or corneal deposit.

Our second Phase 3 registration trial, named “Rocket 2,” is designed to measure efficacy over three months and safety over 12 months. The Rocket 2 trial includes Rhopressa™ dosed both once-daily, or QD, and twice daily, or BID. After evaluating Rocket 1 efficacy results, we obtained agreement from the FDA to change the IOP range for the primary endpoint for the Rocket 2 trial to baseline IOP below 25 mmHg. This modified clinical endpoint range was set to a level where Rocket 1 would have been successful.

In September 2015, the Rocket 2 trial achieved its primary efficacy endpoint of demonstrating non-inferiority of IOP lowering for Rhopressa™ QD and BID compared to timolol BID. The baseline IOPs tested in the trial ranged from pre-study baseline IOPs of above 20 mmHg to below 25 mmHg. The study included a Rhopressa™ BID arm at the request of the FDA, because it is known that PGAs are less efficacious when dosed BID, and we believe there was interest in discovering how Rhopressa™ BID would perform. Baseline IOP was measured prior to treatment. Following treatment, IOP was measured at 8 a.m., 10 a.m.

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and 4 p.m. at the end of week two, week six and day 90. The trial included 129 patients in the Rhopressa™ QD arm, 132 patients in the Rhopressa™ BID arm and 142 patients in the timolol twice-daily arm. The most common Rhopressa™ adverse event in the QD arm was conjunctival hyperemia, or eye redness, which was reported as 35% increased incidence, of which 83% was mild and 16% moderate. Other ocular adverse events occurring in approximately 5% to 15% of patients in the Rhopressa™ QD arm included conjunctival hemorrhage, corneal deposits and blurry vision. The Rhopressa™ BID arm showed slightly higher efficacy, but had a higher incidence of adverse events which led to a greater number of early terminations in comparison to the Rhopressa™ QD arm. Other ocular adverse events occurring in approximately 5% to 17% of patients in the Rhopressa™ QD arm included conjunctival hemorrhage, corneal deposits, blurry vision, increased lacrimation, reduced visual acuity, eye pruritus, and conjunctival edema. In February 2016, safety data for the 12-month period of the Rocket 2 trial confirmed this positive safety profile for the drug and demonstrated a consistent IOP lowering effect throughout the 12-month period at the 8 a.m. timepoint.

After detailed analysis of the Rocket 1 and Rocket 2 results, we observed higher levels of IOP lowering for Rhopressa™ at week two and to a lesser extent at week six stemming from patients who were previously on a PGA, pointing to the potential synergistic effect of PGAs and Rhopressa™, which decreases over the 90-day period as the residual PGA effect subsides. For all other patients, the IOP lowering was consistent across the 90 day measurement periods. For illustrative purposes, the graphic below shows the performance of Rocket 1 and Rocket 2 at baselines above 20 mmHg and below 25 mmHg, compared to timolol.

In addition to our Rocket 1 and Rocket 2 trials, we are currently conducting a one year, safety-only study for Rhopressa™ in Canada, named “Rocket 3,” which commenced in September 2014, and an additional Phase 3 registration trial for Rhopressa™, named “Rocket 4,” which commenced in September 2015. Rocket 4 is designed to gain adequate six-month safety data for regulatory filings in Europe. Based upon discussions with the FDA, we expect to file a NDA for Rhopressa™ in the third quarter of 2016, utilizing Rocket 2 as the pivotal clinical trial and Rocket 1 as supportive. Neither Rocket 3 nor Rocket 4 is required for the NDA filing.

Rhopressa™ Preclinical Anti-Fibrotic and Perfusion Results

We continue to explore the potential longer-term impact of Rhopressa™ on the trabecular meshwork. By increasing trabecular outflow, as demonstrated in our preclinical studies, Rhopressa™, has the potential to stop the degeneration of outflow tissues. As part of the aging process, the trabecular meshwork becomes stiffened and clogged as fibrosis develops and progresses. Preclinical studies on human trabecular meshwork cells have demonstrated a meaningful anti-fibrotic effect from Rhopressa™. Further, additional preclinical experiments on human eyes have demonstrated the product candidate’s potential ability to increase the perfusion of the trabecular meshwork and downstream outflow tissues. We believe this is possible because as a

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result of the action of Rhopressa™ the trabecular meshwork becomes relaxed and opens, which increases the flow of eye fluid, or aqueous humor. This has the potential to increase the health of the trabecular outflow tissues, since it should increase the delivery of nutrients and antioxidants to the trabecular meshwork that were otherwise blocked from passage. The flow of fluid through the trabecular meshwork is the only known mechanism for delivering such nutrients to the diseased tissue, as there are no blood vessels present. Work is continuing as we explore whether our product candidates may be able to prevent, or possibly even reverse, damage to the trabecular meshwork pathway through this potential effect as well as the potential anti-fibrotic effect of our product candidates. If findings are positive and there is demonstrated disease modification, this could be a major breakthrough in the treatment of glaucoma and ocular hypertension.

Roclatan™

Our once-daily, quadruple-action product candidate Roclatan™ is a combination of our triple-action compound AR-13324, the active ingredient in Rhopressa™, formulated with latanoprost in a single eye drop. If approved, we believe that Roclatan™ would be the first glaucoma product to lower IOP through all currently known MOAs:

- increasing fluid outflow through the TM, the eye's primary drain,
- reducing fluid production in the eye,
- reducing EVP, and
- through the MOA of latanoprost, increasing fluid outflow through the uveoscleral pathway, the eye's secondary drain.

Roclatan™ Phase 3 Development Strategy

Our Phase 3 registration trials commenced in September 2015. We anticipate a total enrollment of approximately 1,840 patients in our Phase 3 registrations trials. Our initial Phase 3 registration trial, named "Mercury 1," is a 12-month safety trial with a 90-day interim efficacy readout, which commenced in September 2015. We expect Mercury 1 topline 90-day efficacy data in the third quarter of 2016 and topline 12-month safety data in the third quarter of 2017. Our second Phase 3 registration trial, named "Mercury 2," is a 90-day efficacy and safety trial, which is expected to commence in March 2016. Both trials are designed to demonstrate the superiority of Roclatan™ to each of its components. If both Mercury 1 and Mercury 2 are successful, we expect to file an NDA for Roclatan™ in the second half of 2017, approximately one year after the NDA filing for Rhopressa™.

We also plan to initiate a third Phase 3 registration trial, named "Mercury 3," in the first half of 2017. Mercury 3 will be designed to compare Roclatan™ to a fixed dose combination product broadly marketed in Europe, which if successful should improve our commercialization prospects in that region.

Roclatan™ Phase 2 Efficacy Results

In June 2014, we completed a 28-day Roclatan™ Phase 2b clinical trial. The baseline IOPs tested in the study ranged from 22 to 36 mmHg and included 297 patients who were treated once daily with Roclatan™ 0.01%, Roclatan™ 0.02%, Rhopressa™ 0.02%, or latanoprost. The primary efficacy endpoint for this Phase 2b clinical trial was statistical superiority of Roclatan™ over each of its components on day 29. Baseline IOP was measured prior to treatment. Following treatment, IOP was measured on day eight, day 14 and day 28 at 8 a.m., 10 a.m. and 4 p.m. We observed statistical superiority over the individual components at all time points.

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Roclatan™ vs. Individual Components
Mean IOP at All Time Points (p<0.001)

Roclatan™ 0.02% lowered mean diurnal IOP on day 29 from 25.1 mmHg at baseline to 16.5 mmHg, a 34% decrease in IOP. Roclatan™ 0.02% was determined to be 1.6 - 3.2 mmHg more efficacious than latanoprost and 1.7 - 3.4 mmHg more efficacious than Rhopressa™.

An additional analysis that compared the response results for patients on day 29 revealed that 50% of Roclatan™ patients compared to 28% of latanoprost patients experienced a 35% or greater decrease in mean diurnal IOP from baseline on day 29. Furthermore, 46% of Roclatan™ patients compared to 18% of latanoprost patients had a mean diurnal IOP of 16 mmHg or less on day 29. From a safety perspective, Roclatan™ was well tolerated. The most common Roclatan™ adverse event was hyperemia, or eye redness, which was reported in 40% of patients. For patients who experienced hyperemia, 80% were observed as mild through biomicroscopy findings. Additionally, there were no systemic drug-related adverse events reported.

We believe Roclatan™, if approved, would be the only glaucoma product that covers the full spectrum of currently known IOP- lowering MOAs, giving it the potential to provide a greater IOP-lowering effect than any currently marketed glaucoma product. Therefore, we believe Roclatan™ could compete with both PGA and non-PGA therapies for patients requiring maximal IOP lowering, including those with higher IOPs and those who present with significant disease progression despite currently available therapies.

Pipeline Opportunities

AR-13154

One of our owned preclinical molecules, AR-13154, has demonstrated the potential for the treatment of wet AMD. This preclinical small molecule inhibits Rho kinase, JAK2 and PDGFR- , and has shown lesion size decreases in a model of wet AMD at levels similar to or better than current market-leading products. If proven out, we may have the potential to provide an entirely new mechanism and pathway to treat this disease. Further, in our preclinical studies, we have seen a promising effect of this molecule on reducing neovascularization in a model of proliferative diabetic retinopathy.

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The graph below depicts the results of a preclinical study designed to show the impact of AR-13154 and Eylea® on laser-induced choroidal neovascularization, or CNV, in rats.

Since AR-13154 is a small molecule with a short half-life, and the aforementioned diseases are located in the back of the eye, a delivery mechanism is needed to deliver the molecule to the back of the eye for a sustained delivery period. As a result, in mid-2015 we established a research collaboration with GrayBug, a drug delivery technology spin-out from Johns Hopkins University. We believe that their biodegradable polymer technology may be effective in facilitating delivery of our small molecules, including AR-13154, over a sustained period, such as six months. The technology may also prove useful in delivering other Aerie molecules to the front of the eye, such as for the purpose of long term IOP lowering.

EG-30

Another small molecule that may benefit from delivery technology is EG-30, a preclinical anti-beta amyloid product candidate that we are researching in collaboration with Ramot at Tel Aviv University. We believe that EG-30, Ramot's product candidate, has the potential for neuroprotection and reduction of geographic atrophy in advanced dry AMD.

Our Strategy

Our goal is to become a leader in the discovery, development and commercialization of innovative pharmaceutical products for the treatment of patients with glaucoma and other diseases of the eye. We believe our product candidates have the potential to address many of the unmet medical needs in the glaucoma market. Key elements of our strategy are to:

Advance the development of our product candidates to approval. We expect to file the NDA for Rhopressa™ (netarsudil ophthalmic solution) 0.02% in the third quarter of 2016, using our successful Rocket 2 clinical trial as the pivotal trial and Rocket 1 data as supportive. This will be a key step in driving this drug to a commercial stage in the United States. Our Rocket 4 trial, which is ongoing, is designed to provide adequate six-month safety data to support a filing with the European MAA by approximately mid-2017.

Our second product candidate, once-daily, quadruple-action Roclatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%, which is a fixed-dose combination of Rhopressa™ and latanoprost, the most commonly prescribed drug for the treatment of patients with glaucoma, successfully completed a Phase 2b clinical trial in patients with open-angle glaucoma and ocular hypertension in June 2014. Our first Phase 3 registration trial for Roclatan™, named "Mercury 1," commenced in September 2015. We expect to commence our second Phase 3 trial for Roclatan™, named "Mercury 2," in March 2016. If both Mercury 1 and Mercury 2 are successful, we expect to file an NDA for Roclatan™ in the second half of 2017, approximately one year after the NDA filing for Rhopressa™. We expect to commence a third Phase 3 registration trial for Roclatan™, named "Mercury 3," in Europe in the first half of 2017, which will be designed to compare Roclatan™ to a fixed dose combination product broadly marketed in Europe, which if successful should improve our commercialization prospects in that region.

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Establish internal sales capabilities to commercialize our product candidates in North America. We own worldwide rights to all indications for our product candidates and we plan to retain commercialization rights in North American markets. Ultimately, if our product candidates are approved, we plan to build a commercial team in North America of approximately 100 sales representatives. We expect our sales organization to target approximately 10,000 high prescribing eye-care professionals throughout North America.

Explore partnerships with leading pharmaceutical and biotechnology companies to maximize the value of our product candidates outside North America. We are exploring the licensing of commercialization rights or other forms of collaboration with qualified potential partners for the commercialization of our product candidates in other territories, including Japan and Europe.

Continue to leverage and strengthen our intellectual property portfolio. We believe we have a strong intellectual property position relating to our product candidates. Our intellectual property portfolio contains U.S. and foreign patents and pending U.S. and foreign patent applications related to composition of matter, pharmaceutical compositions and methods of use for our product candidates. We have patent protection for our primary product candidates in the United States through at least 2030.

Expand our product portfolio through internal discovery efforts and in-licensing or acquisitions of additional ophthalmic product candidates or products. We continue to seek to discover and develop new compounds in our research laboratories and employ a scientific staff with expertise in medicinal chemistry, analytical chemistry, biochemistry, cell biology, pharmacology and pharmaceutical science. In addition, we also plan to continue to evaluate the expansion of our product portfolio through in-licensing or acquisitions of additional ophthalmic product candidates or products. We currently have research collaboration arrangements with GrayBug Inc., for drug delivery technology, and Ramot at Tel Aviv University Ltd., for a small molecule anti-beta amyloid product candidate with the potential for neuroprotection and treatment of advanced dry AMD.

Glaucoma Overview

Glaucoma is generally characterized by relatively high IOP as a result of impaired drainage of fluid, known as aqueous humor, from the eye. The FDA recognizes sustained lowering of IOP, measured in terms of mmHg, as the primary clinical endpoint for regulatory approval, making clinical trials for this indication relatively straight-forward due to easily measured objective parameters.

In a healthy eye, aqueous humor is continuously produced and drained from the eye in order to maintain pressure equilibrium and provide micronutrients to various tissues in the eye. The normal range of IOP is generally between 10 and 21 mmHg. Several studies have demonstrated that the significant majority of glaucoma patients have IOPs below 26 mmHg at the time of diagnosis. An insufficient drainage of fluid can increase IOP above normal levels, which can eventually cause damage to the optic nerve. Once damaged, the optic nerve cannot regenerate and thus, damage to vision is permanent.

The most common form of glaucoma is open-angle glaucoma, which is characterized by abnormally high IOP as a result of impaired drainage of fluid from the eye’s primary drain, the TM. Open-angle glaucoma is a progressive disease leading to vision loss and blindness for some patients as a result of irreversible damage to the optic nerve. Studies of the disease have demonstrated that reducing IOP in patients with glaucoma can help slow or halt further damage to the optic nerve and help preserve vision. Once diagnosed, glaucoma requires life-long treatment to maintain IOP at lower levels based on the individual patient’s risk of disease progression. Ophthalmologists will routinely determine a target IOP, which represents the desired IOP level to achieve with glaucoma therapy for an individual patient. Should the disease progress even once the initial target IOP is reached, further lowering of the IOP has been shown to help in preventing additional damage to the optic nerve and further vision loss. This may require lowering IOP until it is in the so-called “low normal range” of 12 to 14 mmHg to protect the optic nerve from further damage.

There are multiple factors that can contribute to an individual getting open-angle glaucoma, including, but not limited to, age, family history and ethnicity. For example, there generally is a higher incidence and severity of the disease in African-American and Hispanic populations.

Some patients with high IOP are diagnosed with a condition known as ocular hypertension. Patients with ocular hypertension have high IOP without the loss of visual fields or observable damage to the optic nerve, and are at an increased risk of developing glaucoma. These patients are commonly treated in the same manner as glaucoma patients.

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The following diagram illustrates how increased IOP eventually leads to increased pressure on the optic nerve, resulting in gradual loss of vision and ultimately visual disability and blindness.

The ciliary body in the eye is the tissue that produces aqueous humor, the production of which is commonly referred to as fluid inflow. The fluid leaves the eye primarily through the TM, the process of which is commonly referred to as fluid outflow. The healthy eye maintains a state of IOP homeostasis through a constant physiological process of aqueous humor production and drainage. The deteriorating function of the TM in glaucoma leads to increased resistance to fluid outflow and higher IOP. There is also a secondary drain for the fluid in the eye known as the uveoscleral pathway, which is typically responsible for approximately 20% of fluid drainage.

In addition to aqueous humor production and drainage through the TM and uveoscleral pathway, EVP plays a significant role in the regulation of IOP. EVP represents the pressure of the blood in the episcleral veins of the eye which are the site of drainage of eye fluid into the bloodstream. Historical studies have shown that EVP accounts for approximately one-half of IOP in normotensive subjects and approximately one-third of IOP in patients with pressures of 24 to 30 mmHg. When EVP is lowered, aqueous humor is able to flow more freely from the eye.

Patients are diagnosed through measurements of IOP using Goldmann applanation tonometry, the standard device used by clinicians to measure IOP, along with an evaluation of visual fields and observing the appearance of the optic nerve. These tests are routinely carried out by eye-care professionals. The initial treatment for patients diagnosed with open-angle glaucoma or ocular hypertension is typically a PGA eye drop. PGAs are designed to lower IOP by increasing outflow through the eye's secondary fluid drain. An eye-care professional will then measure a patient's response to the drug over the first few months. It has been shown that up to 50% of glaucoma patients require more than one drug to treat their IOP. This may occur as early as three to six months after initiating treatment with a PGA. The eye-care professionals may then add a second drug from one of the non-PGA classes, to be used together with the initial drug, or switch to a fixed-combination of two drugs in a single eye drop, or select an alternative single treatment. The reason so many patients eventually need more than one drug is generally considered to be a reflection of the progressive nature of the disease at the TM.

In severe glaucoma cases, patients may need to undergo an invasive surgical procedure. Trabeculectomy is the most common glaucoma-related surgical procedure, also referred to as filtration surgery, in which a piece of tissue in the drainage angle of the eye is removed, creating an opening to the outside of the eye. The opening is partially covered with a scleral flap, the white part of the eye, and the conjunctiva, the thin membrane covering the sclera. This new opening allows fluid to drain out of the eye, bypassing the clogged drainage channels of the TM to maintain a lowered IOP. Devices called shunts are used in glaucoma surgery to divert fluid in a controlled manner from the inside of the eye to the subconjunctival space bypassing the blocked TM. Generally, the shunts reduce IOP to the extent that the use of drops can be reduced, but often not completely eliminated. Many patients continue to require eye drops even following surgery.

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 Valeant Pharmaceuticals International, Inc., Novartis International AG, Allergan, Inc., Santen 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 or technologies to treat glaucoma or other diseases of the eye. Any product candidates that we

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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 current product candidates, if approved, are likely to be efficacy and MOAs, safety, convenience, price, tolerability and the availability of reimbursement from government and other third-party payors.

We expect to compete directly against companies producing existing and future glaucoma treatment products. The most commonly approved classes of eye drops to lower IOP in glaucoma are discussed below:

PGA Drug Class

- Prostaglandin Analogues (PGAs). Most PGAs are once-daily dosed eye drops generally prescribed as the initial drug to reduce IOP by increasing fluid outflow through the eye's secondary drain. They do not target the diseased tissue, or TM. PGAs represent approximately one-half of the U.S. and European prescription volume for the treatment of glaucoma.

Xalatan (latanoprost), the best-selling PGA, together with Xalacom, its fixed-combination with a beta blocker, which is not available in the United States, had worldwide peak sales of approximately $1.7 billion before its patent expired in 2012, according to publicly reported sales. The adverse effects of PGAs include hyperemia or eye redness, irreversible change in iris color, discoloration of the skin around the eyes, and droopiness of eyelids caused by the loss of orbital fat. PGAs should be used with caution in patients with a history of intraocular inflammation.

Non-PGA Drug Class

- Beta Blockers. Beta blockers, with their MOA designed to inhibit aqueous production, are one of the oldest approved drugs for the lowering of IOP. The most commonly used drug in this class is timolol. Beta blockers are less effective than PGAs in terms of IOP lowering and are typically used twice daily. Beta blockers are the most commonly used non-PGA drug. They are used as an initially prescribed monotherapy and as an adjunct therapy to PGAs when the efficacy of PGAs is insufficient. Beta blocker eye drops have contraindications in their label as a result of systemic exposure from topical application of the eye drops, potentially leading to cardio-pulmonary events such as bronchospasm, arrhythmia and heart failure.
- Carbonic Anhydrase Inhibitors. Carbonic anhydrase inhibitors, with their MOA designed to inhibit aqueous production, are less effective than PGAs and are required to be dosed three times daily in order to obtain the desired IOP lowering. In published clinical studies of carbonic anhydrase inhibitors, the most frequently reported adverse events reported were blurred vision and bitter, sour or unusual taste. Carbonic anhydrase inhibitors are sulfonamides and, as such, systemic exposure increases risk of adverse responses such as Stevens Johnson syndrome and blood dyscrasias.
- Alpha Agonists. Alpha agonists, with their MOA designed to inhibit aqueous production plus have an effect on uveoscleral outflow, are less effective than PGAs and need to be dosed three times daily in order to obtain the desired IOP lowering. In clinical studies, the most frequently reported adverse reactions that occurred in individuals receiving brimonidine ophthalmic solution, a commonly prescribed alpha agonist, included allergic conjunctivitis, conjunctival hyperemia, eye pruritus, burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness and visual disturbance.

Despite their modest efficacy, safety and tolerability profiles, the requirement for two to three doses per day, and the fact that they do not target the diseased tissue in glaucoma, the beta blocker, carbonic anhydrase inhibitor and alpha agonist products account for up to one-half of the total prescription volume for the treatment of glaucoma based on historical prescription patterns, with beta blocker timolol being the most widely prescribed non-PGA drug. This is driven by the PGA products not being sufficiently effective as monotherapy for up to half of all glaucoma patients.

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New eye drops for the treatment of glaucoma continue to be developed by our competitors. The following table outlines publicly disclosed development programs for the treatment of glaucoma of which we are aware.

New MOAs

Brand	MOA / Dosing	Trial Stage
Rhopressa™ (Aerie AR-13324)	ROCK/NET inhibitor (qd)	Phase 3
Roclatan™ (Aerie PG324)	ROCK/NET inhibitor + PGA (qd)	Phase 3
INO-8875 (Inotek)	Adenosine-A1 agonist (bid or qd)	Phase 3
OPA-6566 (Acucela)	Adenosine-A2a agonist (bid)	Phase 1/2
SYL040012 (Sylentis)	RNAi beta blocker (qd)	Phase 2

New PGAs[1]

Brand	MOA / Dosing	Trial Stage
Vesneo (Bausch + Lomb)	NO donating latanoprost (qd)	Filed NDA
DE-117 (Santen)	EP2 agonist (qd)	Phase 2
ONO-9054 (Ono)	FP/EP3 agonist (qd)	Phase 2

[1]Not usable as add-on therapy to current PGAs.

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. In July 2015, Bausch + Lomb Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International, Inc., filed a NDA for a nitric oxide-donating latanoprost, which is currently under review by the FDA for the treatment of open angle glaucoma and ocular hypertension. Early-stage companies are also developing treatments for glaucoma and other diseases of the eye and may prove to be significant competitors, such as Inotek Pharmaceuticals, which is developing an adenosine receptor agonist. We expect that our competitors will continue to develop new treatments for glaucoma and other diseases of they eye, which may include eye drops, oral treatments, surgical procedures, implantable devices or laser treatments. Alternative treatments beyond eye drops continue to develop.

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 insurers or other third-party payors encourage the use of generic products. Our industry is highly competitive and is currently dominated by generic drugs, such as latanoprost and timolol, in the case of glaucoma treatment, 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

AR-13324, the active ingredient in Rhopressa™, is a small molecule and capable of being manufactured in reliable and reproducible synthetic processes from readily available starting materials. We believe the chemistry used to manufacture AR-13324, Rhopressa™ and Roclatan™ is amenable to 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 any of these or any other third-party suppliers to support our clinical trials. Latanoprost, used in the manufacture of Roclatan™, is 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

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that there are a number of potential replacements, although we might experience a delay in our ability to obtain alternative suppliers.

With respect to commercial production of our potential products in the future, we plan on outsourcing the production of the active pharmaceutical ingredients. The commercial production of our final drug product manufacturing is expected to be supported by a combination of internal and outsourced manufacturing. We are currently evaluating the possibility of constructing our own manufacturing plant in Ireland. In addition, we have entered into a contractual relationship for the final drug product manufacturing for commercialization. However, we do not have any current contractual relationships for the commercial production of the active pharmaceutical ingredients.

We expect to continue to develop drug candidates that can be produced cost-effectively 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

We have obtained patent protection for our primary product candidates, Rhopressa™ and Roclatan™ (patent protection for Roclatan™ arises from the patent protection we have secured for Rhopressa™), in the United States and certain foreign jurisdictions and are seeking patent protection in a number of other foreign jurisdictions for these product candidates. We intend to maintain and defend our patent rights to protect our technology, inventions, processes and improvements that are commercially important to the development of our business. We cannot be sure that any of our existing patents or patents we obtain in the future will be commercially useful in protecting our technology. We cannot be sure that our patents will issue on any of our pending patent applications or patent applications we file in the future. Our commercial success also depends in part on our non-infringement of the patents or proprietary rights of third parties. For a more comprehensive discussion of the risks related to our intellectual property, see “Risk Factors-Risks Related to Intellectual Property.”

Our intellectual property consists of issued patents, and pending patent applications for compositions of matter and methods of use, for our product candidates and other proprietary technology. For our primary product candidates Rhopressa™ and Roclatan™, we hold U.S. Patent 8,450,344, which is scheduled to expire in 2026, and U.S. Patent 8,394,826, which is scheduled to expire in 2030, each of which has claims directed to composition of matter and method of use. We hold patents for composition of matter and method of use in certain foreign jurisdictions for our primary product candidates. Additionally, we hold patents for other ROCK Inhibitor molecules.

We have established and continue to build proprietary positions for our product candidates and related technology in the United States and other jurisdictions. As of December 31, 2015, we had 58 United States or foreign issued patents that cover various aspects of our current and previously discontinued product candidates and our other proprietary technology and 27 U.S. patent applications or foreign patent applications that, if patents were to issue based on the existing claims, would cover various aspects of our current and previously discontinued product candidates and our other proprietary technology.

Aerie® is a registered trademark of ours and we have applications pending from the U.S. Patent and Trademark Office, or USPTO, for the registration of our trademarks Rhopressa™ and Roclatan™.

Regulatory Matters

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 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.

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The FDA and comparable regulatory agencies in state and local jurisdictions and in foreign countries impose substantial requirements upon the clinical development, manufacture 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 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, Good Clinical Practices, or GCP, which are international ethical and scientific quality standards meant to assure the rights, safety and well-being of trial participants are protected and to define the roles of clinical trial sponsors, administrators, and monitors;
- pre-approval inspection of manufacturing facilities and clinical trial sites; and
- FDA approval of an NDA, which must occur before a drug can be marketed or sold.

IND and Clinical Trials

Prior to commencing the first clinical trial, an initial IND, which contains the results of preclinical tests 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 conduct of the clinical trial. In such a case, the IND sponsor must resolve any outstanding concerns with the FDA before the clinical trial may begin. 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 proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that site. Informed 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. Throughout this report, we refer to our initial Phase 2 clinical trials as "Phase 2a clinical trials" and our subsequent Phase 2 clinical trials as "Phase 2b 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 registration trials, Phase 3 registration 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 performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and 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

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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.

An investigational drug product that is a combination of two different drugs in the same dosage form must comply with an additional rule that requires that each component make a contribution to the claimed effects 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 discuss 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. 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 (currently exceeding $2,350,000 for fiscal year 2016) unless a waiver or exemption applies. The application includes all relevant data available from pertinent non-clinical, preclinical 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 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 registration trial that they believe will support approval of the new drug.

Concurrent with clinical trials, companies usually complete additional animal safety studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in accordance with current Good Manufacturing Practice, or cGMP, requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drugs. 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.

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 files them. 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 files it. The FDA has

60 days from its receipt of an NDA to conduct an initial review to determine whether the application will be filed based on the agency's threshold determination that the application is sufficiently complete to permit substantive review. If the NDA submission is filed, 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 in 12 months from

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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 initial 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 will 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 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 now has express statutory 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 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 if consensus is not obtained until after the PDUFA review cycle, 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 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 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 U.S. 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

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restored. The Hatch-Waxman Amendments also provide a process for listing patents pertaining to approved products in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) and for a competitor seeking approval of an application that references a product with listed patents to make certifications pertaining to such patents. In addition, the Hatch-Waxman Amendments provide for a statutory protection, known as non-patent exclusivity, against the FDA's acceptance or approval of certain competitor applications.

Patent Term Restoration

Patent term restoration can compensate for time lost during product development and the regulatory review process 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.

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims covering the applicant's product or method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug are then published in the FDA's Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown to be bioequivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, preclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA applicant may also elect to submit a Section VIII statement certifying that its proposed ANDA labeling does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been filed by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

An applicant submitting an NDA under Section 505(b)(2) of the FDCA, which permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant and for which the applicant has not obtained a right of reference, is required to certify to the FDA regarding any patents listed in the Orange Book for the approved product it references to the same extent that an ANDA applicant would.

Market Exclusivity

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain 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, or NCE. A drug is entitled to NCE exclusivity if it contains a drug substance no active moiety of which has been previously approved by the FDA. This means that, in the case of a fixed-dosed combination product, the FDA makes the NCE exclusivity determination for each drug substance in the drug product and not for the drug product as a whole. During the exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA submitted

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by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a Paragraph IV certification. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing NDA 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, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs for the original conditions of use, such as the originally approved indication. 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.

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 (known as "off-label use"), limitations on industry-sponsored scientific and educational activities and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers 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 in 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 manufacture 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, currently exceeding $100,000 per product and $550,000 per establishment for fiscal year 2016. These fees are typically increased annually.

The FDA also may require post-marketing testing, also known as Phase 4 testing, REMS to monitor the effects of an approved product or place conditions on an approval 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.

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Reimbursement, Anti-Kickback and False Claims Laws and Other Regulatory Matters

In the United States, the research, manufacturing, distribution, sale and promotion of drug products and medical devices are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare & Medicaid Services, other divisions of the U.S. 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. For example, sales, marketing and scientific/educational grant programs must comply with the Federal Anti-Kickback Statute, the False Claims Act, as amended, the privacy regulations promulgated under the Health Insurance Portability and Accountability Act (HIPAA), as amended, 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 Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide 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. Unlike Medicare Part A and B, part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered 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. Any formulary used by a part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic 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 products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA 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 the MMA may result in a similar reduction in payments from non-government payors.

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 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 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 candidate, if any such product or the condition that it is intended to treat is the subject of a trial. It is also possible that comparative effectiveness research demonstrating benefits in a competitor’s product could adversely affect the sales of our product candidate. 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.

As noted above, in the United States, we are subject to complex laws and regulations pertaining to healthcare “fraud and abuse,” including, but not limited to, the Federal Anti-Kickback Statute, the Federal False Claims Act, and other state and federal laws and regulations. The Federal Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is

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intended to induce the referral of business, including the purchase, order, or prescription of a particular drug, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. 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, the absence of guidance in the form of regulations or court decisions, and the potential for additional legal or regulatory change in this area, it is possible that our future sales and marketing practices and/or our future relationships with eye-care professionals might be challenged under anti-kickback laws, which could harm us. Because we intend to commercialize products that could be reimbursed under a federal healthcare program and other governmental healthcare programs, we plan to develop a comprehensive compliance program that establishes internal controls to facilitate adherence to the rules and program requirements to which we will or may become subject.

The Federal False Claims Act prohibits anyone from 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, 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 False Claims Act in connection with their off-label promotion of drugs. Penalties for a 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 False Claims Act and certain states have enacted laws modeled after the Federal False Claims Act.

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, beginning in 2013, a similar federal requirement will require manufacturers to track and report to the federal government certain payments made to physicians and teaching hospitals made in the previous calendar year. 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 soon federal, authorities.

The failure to comply with regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by required, 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.

Patient Protection and Affordable Care Act

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, PPACA) was enacted, which includes measures that have or will significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of PPACA 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 Department of Health and Human Services a condition for states to receive federal matching funds for the manufacturer's covered outpatient drugs furnished to Medicaid patients. Effective in 2010, PPACA made several changes to the Medicaid Drug Rebate Program,

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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 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. PPACA also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization as of 2010 and by, beginning in 2011, expanding the population potentially eligible for Medicaid drug benefits. The Centers for Medicare & Medicaid Services, or CMS, expanded Medicaid rebate liability to the territories of the United States as well, effective April 1, 2017. In addition, PPACA provides for the public availability of retail survey prices and certain weighted average AMPs under the Medicaid program. The implementation of this requirement by the CMS, beginning in April 2016, may also provide for the public availability of pharmacy acquisition of cost data, which could negatively impact our sales.

- In order for a pharmaceutical product to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. Effective in 2010, PPACA expanded the types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs when used for the orphan indication. In addition, as 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.
- Effective in 2011, PPACA 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 patients in the coverage gap (i.e., "donut hole").
- Effective in 2011, PPACA 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.
- PPACA requires pharmaceutical manufacturers to track certain financial arrangements with physicians and teaching hospitals, including any "transfer of value" made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers were required to track this information beginning in 2013, and the first reports were due in 2014. The information reported each year is made publicly available on a searchable website.
- As of 2010, a new Patient-Centered Outcomes Research Institute was established pursuant to PPACA 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.
- PPACA 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.
- PPACA established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

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

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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 a marketing authorization 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 European Union, 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 in each of the EU countries where the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. In addition, all suspected unexpected 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 27 Member States of the European Union plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations: the Community MA, 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 MA, 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 European Union. The National MA 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 MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MA 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 MA 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 MA in all the Member States where the authorization was sought. Before granting the MA, 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. In addition, our international operations and relationships with partners, collaborators, contract research organizations, vendors and other agents are subject to anti-corruption and anti-bribery laws and regulations, including the U.S. Foreign Corrupt Practices Act ("FCPA"), which prohibits U.S. companies and their representatives from engaging in bribery or other prohibited payments to foreign officials for the purpose of obtaining or retaining business. Failure to comply with the FCPA, or similar applicable laws and regulations in other countries, could expose us and our personnel to civil and criminal sanctions. We may incur significant costs to comply with such laws and

regulations now or in the future.

Employees

We had 70 full-time employees as of December 31, 2015. None of our employees are represented by any collective bargaining unit. We believe that we maintain good relations with our employees.

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Corporate and Available Information

Our principal executive offices are located at 2030 Main Street, Suite 1500, Irvine, California 92614 and our telephone number is (949) 526-8700. We were incorporated in Delaware in June 2005. Our internet address is www.aeriepharma.com. 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.

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ITEM 1A. RISK FACTORS

We operate in an industry that involves numerous risks and uncertainties. The risks and uncertainties described below are not the only ones we face. Other risks and uncertainties, including those that we do not currently consider material, may impair our business. If any of the risks discussed below actually occur, our business, financial condition, operating results or cash flows could be materially adversely affected. This could cause the trading price of our common stock to decline.

Risks Related to Development, Regulatory Approval and Commercialization

We depend substantially on the success of our product candidates, particularly Rhopressa™ and Roclatan™, which are still in development. If we are unable to successfully commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

Our business and the ability to generate revenue related to product sales, if ever, will depend on the successful development, regulatory approval and commercialization of our product candidates for the treatment of patients with glaucoma and other diseases of the eye, particularly Rhopressa™ and Roclatan™, which are still in development, and other potential products we may develop or license. 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;
- receipt of regulatory approvals from applicable regulatory authorities;
- establishment of internal manufacturing capacity or 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;
- obtaining reimbursement from third-party payors for product candidates, if and when approved;
- competition with other products; and
- continued acceptable safety 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 commercialize our product candidates, which could materially harm our business and we may not be able to earn sufficient revenues and cash flows to continue our operations.

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

Phase 3 trials for Rhopressa™ commenced in July 2014 and we completed our initial Phase 3 registration trial, named “Rocket 1,” which was designed to measure efficacy over three months. The Rocket 1 trial did not meet its primary efficacy endpoint of demonstrating non-inferiority of intraocular pressure, or IOP, lowering for once-daily Rhopressa™ compared to twice-daily timolol, but did achieve its pre-specified secondary endpoint. We evaluated the data and results from Rocket 1 and obtained agreement from the FDA to change the IOP range used for the primary endpoint of our second Phase 3 registration trial, named “Rocket 2,” which is designed to measure efficacy over three months and assess safety over 12 months. The modified clinical endpoint range for Rocket 2 was set to a level where Rocket 1 would have been successful. In September 2015, the Rocket 2 trial achieved its primary efficacy endpoint of demonstrating non-inferiority of Rhopressa™ compared to timolol. In addition, the recently reported topline 12-month

safety data from Rocket 2 confirmed a positive safety profile for the drug and demonstrated a consistent IOP lowering effect throughout the 12-month period at the specified timepoint. We are also currently conducting a one year, safety-only study in Canada, named “Rocket 3,” and an additional Phase 3 registration trial for

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Rhopressa™, named “Rocket 4,” which commenced in September 2015. Rocket 4 was initiated by Aerie in part to gain adequate safety data for regulatory filings in Europe. Based upon recent discussions with the FDA, we expect to submit a new drug application (“NDA”) for Rhopressa™ in the third quarter of 2016 utilizing Rocket 2 as the pivotal clinical trial and Rocket 1 as supportive in nature. We do not anticipate that completion of Rocket 4 will be necessary prior to submitting the NDA.

The first Phase 3 registration trial for Roclatan™, named “Mercury 1,” commenced in September 2015. We expect to commence our second Phase 3 registration trial for Roclatan™, named “Mercury 2,” in the first quarter of 2016. If both of these trials are successful, we expect to file our NDA for Roclatan™ in the second half of 2017, approximately one year behind Rhopressa™. We also plan to initiate a third Phase 3 registration trial in Europe, named “Mercury 3,” in the first half of 2017. Mercury 3 will be designed to compare Roclatan™ to a broadly marketed fixed dose combination product in Europe.

We cannot predict whether these trials and future trials will be successful or whether regulators will agree with our conclusions regarding the preclinical studies and clinical trials we have conducted to date.

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 an 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 file the NDA or refuse to file the NDA. We cannot be certain that any submissions will be filed by the FDA.

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 foreign regulatory approval could require additional non-clinical studies or clinical trials, which could be costly and time consuming. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. For all of these reasons, we may not obtain foreign 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 studies 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.

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. If regulatory authorities require additional time or studies to assess the safety or efficacy of our product candidates, we may require funding beyond the amounts currently on our balance sheet. In addition, in the event of any unforeseen costs or other business decisions, 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;

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- regulatory requests for additional analyses, reports, data, non-clinical and preclinical studies and clinical trials;
- regulatory questions 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 non-U.S. regulators regarding the scope or design of our clinical trials;
- our inability to enroll a sufficient number of patients who meet the inclusion and exclusion criteria in our clinical trials;
- our inability to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- unfavorable or inconclusive results of clinical trials and supportive non-clinical studies, including unfavorable results regarding effectiveness of product candidates during clinical trials;
- 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 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 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;
- our inability to obtain approval from institutional review boards to conduct clinical trials at their respective sites;
- our inability to timely manufacture or obtain from third parties sufficient quantities or quality of the product candidate or other materials required for a clinical trial; and
- difficulty in maintaining contact with patients after treatment, resulting in incomplete data.

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 institutional review boards for re-examination, which may impact the costs, timing or successful completion of a clinical trial.

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.

Failure can occur at any stage of clinical development. If the clinical trials for our current and potential future 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 Phase 3 clinical trials that may 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 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. Our future clinical trial results therefore may not demonstrate safety and efficacy sufficient to obtain regulatory approval for our current and potential future product candidates.

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Flaws in the design of a clinical trial may not become apparent until the clinical trial is well-advanced or after data results have been obtained. 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 potential products.

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, institutional review boards or data safety monitoring boards may at any time order 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. Since our inception, we have not voluntarily or involuntarily suspended or terminated a clinical trial due to unacceptable safety risks 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, analyses and entry criteria, 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. Our clinical trials for our primary product candidates, Rhopressa™ and Roclatan™, may not produce the results that we expect and remain subject to the risks associated with clinical drug development as indicated above.

Several companies have previously pursued ROCK inhibitors for ophthalmic use but to date no ROCK inhibitors have been approved and most of those companies have chosen to discontinue clinical development of their ROCK inhibitors. One of our ROCK inhibitors, AR-12286, was discontinued in the clinical stage of development due to an inability to maintain its effectiveness over time. In a 28-day Phase 2b clinical trial, AR-12286 lowered IOP by 6.7 mmHg on day seven, but lowered IOP by only 5.3 mmHg on day 28. This trend continued in a follow-up three-month study. As a result, in June 2013 we discontinued any further clinical development of AR-12286 and its fixed-dose combination product PG286.

In April 2015, we announced that Rocket 1 did not meet its primary efficacy endpoint of demonstrating non-inferiority of IOP lowering for once-daily Rhopressa™ compared to twice-daily timolol, but did achieve its pre-specified secondary endpoint. We evaluated the data and results from Rocket 1 and obtained agreement from the FDA to change the IOP range used for the primary endpoint of Rocket 2 which is designed to measure efficacy over three months and assess safety over 12 months. The modified clinical endpoint range for Rocket 2 was set to a level where Rocket 1 would have been successful. In September 2015, the Rocket 2 trial achieved its primary efficacy endpoint of demonstrating non-inferiority of Rhopressa compared to timolol. In addition to successfully achieving non-inferiority to timolol at this endpoint range, the recently reported topline 12-month safety data from Rocket 2 confirmed a positive safety profile for the drug and demonstrated a consistent IOP lowering effect throughout the 12-month period at the specified timepoint.

If based on the clinical results of Rhopressa™, we discontinue the advancement of this product candidate, in certain circumstances we may similarly determine not to advance Roclatan™, which combines Rhopressa™ with latanoprost. Additionally, our clinical trials are designed to test the use of Rhopressa™ and Roclatan™ as a monotherapy, rather than as an add-on therapy. Accordingly, the efficacy of our primary product candidates may not be similar or correspond directly to their efficacy when used as an add-on therapy, which we expect will be a primary use of Rhopressa™.

In February 2014, we reported the results of a preclinical animal study sponsored by Aerie, whereby the administration of Rhopressa™ eye drops demonstrated statistically significant reductions in EVP and IOP in rabbits following the third daily dose. Based on the results of this preclinical study, together with the consistent IOP-lowering effect of Rhopressa™ demonstrated in our prior clinical trials, we believe the reduction of EVP is an additional MOA of Rhopressa™ and Roclatan™. However, like the other differentiated MOAs of our product candidates, increasing

outflow through the TM and decreasing fluid production in the eye, our product candidates' effect on EVP has not been studied in humans and neither our ongoing, nor our planned, Phase 3 registration trials for Rhopressa™ or Roclatan™ will be designed to demonstrate reduction of EVP or other MOAs of our product candidates. If we are not able to demonstrate to the satisfaction of the FDA and relevant non-U.S. regulators the reduction of EVP, or any of the other differentiated MOAs of our product candidates, even if we otherwise obtain regulatory approval for Rhopressa™ and Roclatan™, it could limit the types of claims we will be able to make in our marketing and labeling of our product candidates.

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We believe Rhopressa™, if approved, will compete against non-PGA products as a preferred adjunctive therapy to PGAs. In addition, if approved, we believe that Rhopressa ™ may also become a preferred therapy in several populations including where patients have low to moderately elevated IOPs at the time of diagnosis. No patients with low-tension glaucoma have been or will be included in these clinical trials, and our expectations with respect to subjects with low IOP are based to a large extent on extrapolation of results for subjects with moderately elevated IOP. Even if our product candidates were to obtain regulatory approval, if we are unable to support claims about our product candidates to the satisfaction of the FDA and relevant non-U.S. regulators, including claims with respect to the efficacy of Rhopressa™ as an adjunctive therapy or for patients with low IOP, it could limit the types of claims we will be able to make in our marketing and product labeling of these product candidates.

In addition to the circumstances noted above, we may experience numerous unforeseen events that could cause our clinical trials to be unsuccessful, delayed, suspended or terminated, or which could delay or prevent our ability to receive regulatory approval or commercialize our current and potential future 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 institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may 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 current and potential future product candidates, our commercial prospects will be adversely impacted and our ability to generate product revenues may be delayed or eliminated.

If we are unable to establish a direct sales force, 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 our product candidates are approved by the FDA for commercial sale, we intend to market directly to eye-care professionals in North America through our own sales force, targeting approximately 10,000 high-prescribing eye-care professionals. If our product candidates are approved in Europe for commercial sale and if we self-commercialize our product candidates in Europe, we will need to establish similar functions or outsource these functions to third parties. 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 eye-care professionals to prescribe any future approved products;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and

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- 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 have international operations and intend to explore the licensing of commercialization rights or other forms of collaboration outside of North America, which will expose us to additional risks of conducting business in international markets.

Markets outside of North America are an important component of our growth strategy. As part of this strategy, in March 2015 and April 2015, we formed Aerie Limited and Aerie Ireland Limited, respectively. If we fail to commercialize, 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 operations and 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 or expand 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;
- 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.

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. To date, the main tolerability finding of Rhopressa™ has been mild hyperemia, or eye redness. We recently reported 12-month safety data from Rocket 2, in which some patients also experienced conjunctival hemorrhages, corneal deposits, blurry vision, and decreased visual acuity as adverse events. Roclatan™ combines Rhopressa™ with latanoprost. To date, the main tolerability finding of Roclatan™ has also been mild hyperemia. The main adverse effects

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of latanoprost include hyperemia, irreversible change in iris color, discoloration of the skin around the eyes and droopiness of eyelids caused by the loss of orbital fat.

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 or other 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;
- 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 revenues from its sale.

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, as well as from academic institutions, government agencies and private and public research institutions, which may in the future develop products to treat patients with glaucoma or other diseases of the eye. 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. In July 2015, Bausch + Lomb Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International, Inc., filed an NDA for a nitric oxide-donating latanoprost, which is currently under review by the FDA for the treatment of open angle glaucoma and ocular hypertension. Additionally, early-stage companies are also developing treatments for glaucoma and other diseases of the eye and may prove to be significant competitors, including Inotek Pharmaceuticals, which is developing an adenosine receptor agonist. We expect that our competitors will continue to develop new treatments for glaucoma and other diseases of the eye, which may include eye drops, oral treatments, surgical procedures, implantable devices or laser treatments. Alternative treatments beyond eye drops continue to develop. For example, although surgical procedures are currently used in severe cases, less invasive procedures are currently under development and we expect that we will compete with other companies that develop implantable devices or other products or procedures for use in the treatment of glaucoma or other diseases of the eye.

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 potential products. We expect that our ability to compete effectively will depend upon, among other things, our ability to:

- successfully complete clinical trials and obtain all requisite regulatory approvals in a timely and cost- effective manner;
-

obtain and maintain patent protection and non-patent exclusivity for our products and otherwise prevent the introduction of generics of our products;

- attract and retain key personnel;
- build an effective selling and marketing infrastructure;

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- demonstrate the advantages of our product candidates compared to alternative therapies, including currently marketed PGA and non-PGA products;
- compete against other products with fewer contraindications; and
- obtain and sustain adequate reimbursement from third-party payors.

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

The commercial success of our potential products will depend on the degree of market acceptance among eye-care professionals, patients, patient advocacy groups, healthcare payors and the medical community.

Our potential products may not gain market acceptance among eye-care professionals, patients, patient advocacy groups, healthcare payors and the medical community. There are a number of available therapies marketed for the treatment of glaucoma and other diseases of the eye. Some of these drugs are branded and subject to patent protection, but most others, including latanoprost and many beta blockers, in the case of glaucoma treatment, are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by eye-care professionals, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. The degree of market acceptance of our potential products will depend on a number of factors, including:

- the market price, affordability and patient out-of-pocket costs of our potential products relative to other available products, which are predominantly generics;
- the effectiveness of our potential products as compared with currently available products;
- patient willingness to adopt our potential products 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;
- limitations or warnings contained in a product candidate’s FDA-approved labeling;
- limitations in the approved clinical indications and MOAs for our product candidates;
- relative convenience and ease of administration;
- the strength of our selling, marketing and distribution capabilities;
- the quality of our relationships with eye-care professionals, patient advocacy groups, third-party payors and the medical community;
- sufficient third-party coverage or reimbursement; and
- potential product liability claims.

In addition, the potential market opportunity for our potential products is difficult to precisely estimate. Our estimates of the potential market opportunity for our potential products include several key assumptions based on our industry knowledge, industry publications, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, independent sources have not verified all of our assumptions. If any of these assumptions proves to be inaccurate, then the actual market for our potential products could be smaller than our estimates of our potential market opportunity. If the actual market for our potential products 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 potential products 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 an adequate level of reimbursement for our potential products by third-party payors, potential future sales would be materially adversely affected.

The course of treatment for glaucoma patients includes primarily 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 potential products without reimbursement from third-party payors, and any reimbursement policy may be affected by future healthcare reform measures. We cannot be certain

that reimbursement will be available for our potential products or any other product candidate we develop for glaucoma or other diseases of the eye. Additionally, even if

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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 United States healthcare industry is toward cost containment. Large public and private payors, managed care organizations, group purchasing organizations and 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 products, 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. If we are unable to show a significant benefit relative to existing generic drugs, Medicare, Medicaid and private payors may not be willing to reimburse for our drugs, which would significantly reduce the likelihood of them gaining market acceptance. 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.

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

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

If we are found in violation of federal or state “fraud and abuse” laws or other healthcare laws and regulations, we may be required to pay a penalty and/or be suspended from participation in federal or state healthcare programs, 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, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer or pay any remuneration that is intended to induce the referral of business, including the purchase, order or prescription of a particular drug for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Although we seek to structure our business arrangements in compliance with all applicable requirements, these laws are broadly written, and it is often 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 Act prohibits anyone 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, claims for items or services that were not provided as claimed, or claims for medically unnecessary items or services. Many states have similar false claims laws. 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. Under the Health Insurance Portability and Accountability Act of 1996, we are prohibited from 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. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines and/or exclusion or suspension from federal and state

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healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the government under the Federal False Claims Act as well as under the false claims laws of several states.

Many states have adopted laws similar to the Federal Anti-Kickback Statute, 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 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 are 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.

Neither the government nor the courts have provided definitive guidance on the application of fraud and abuse laws to our business. 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. While we believe we have structured our business arrangements to comply with these laws, 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, exclusion from governmental funded federal or state healthcare programs 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.

Recently enacted and future legislation may increase the difficulty and cost of commercializing our potential products 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 potential products, restrict or regulate post-marketing activities and affect our ability to profitably sell our potential products for which we obtain regulatory approval.

In the United States, the MMA changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly by establishing Medicare Part D and introduced a reimbursement methodology based on average sales prices for physician-administered drugs under Medicare Part B. In addition, this legislation provided authority for limiting the number of drugs that are covered in any therapeutic class under the Part D program. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and reimbursement rate that we receive for any of our approved products. While the MMA only applies to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

In March 2010, President Obama signed into law the PPACA, a sweeping law intended to 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. PPACA 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. The Centers for Medicare & Medicaid Services, which administers the Medicaid Drug Rebate Program, also expanded Medicaid rebates to the utilization that occurs in the territories of the United States, such as Puerto Rico and the Virgin Islands, effective April 1, 2017. Further, beginning in 2011, PPACA imposed a significant annual fee on companies that manufacture or import branded prescription drug products and

requires manufacturers to provide a 50% discount off the negotiated price of prescriptions filled by beneficiaries in the Medicare Part D coverage gap, referred to as the “donut hole.” Substantial new provisions affecting compliance have also been enacted, which may require us to modify our business practices with healthcare practitioners. For example, pharmaceutical companies are required to track certain payments made to physicians and teaching hospitals, and the first reports were due in 2014 and the reported information was made publicly available on a searchable website in September 2014. We will not know the full effects of PPACA until applicable federal and state agencies issue regulations or guidance under the new law. Although it is too early to determine the full effect of PPACA, the new law appears likely to continue the downward pressure on

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pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

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.

If we face allegations of noncompliance with the law and encounter sanctions, our reputation, revenues and liquidity may suffer, and our potential 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 potential 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.

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 manufacturing facilities are required to comply with extensive FDA and 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 cGMPs. 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 and EMA and other similar agencies and to comply with certain requirements concerning advertising and promotion for our potential products. 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, uses or claims 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 potential products fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters or untitled letters;
- require product recalls;
-