AERIE PHARMACEUTICALS INC
Form 10-K
March 26, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2013

or

¨ **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.)**

135 US Highway 206, Suite 15

Bedminster, New Jersey 07921

(908) 470-4320

(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 ¨ No x

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

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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files): Yes x No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of 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. x

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

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

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

The aggregate market value of the voting stock held by non-affiliates of the registrant on October 25, 2013, based upon the closing price of $10.61 of the registrant s common stock as reported on the NASDAQ Global Market, was $79,913,000. The registrant has elected to use October 25, 2013, as the calculation date, which was the initial trading date of the registrant s common stock on the NASDAQ Global Market, because on June 28, 2013 (the last business day of the registrant s most recently completed second fiscal quarter), the registrant was a privately held company.

As of March 19, 2014, the registrant had 23,316,653 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 2014 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, 2013.

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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, could, might, will, should or other words that convey uncer 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 Phase 3 and Phase 2b clinical trials for our current product candidates, including statements regarding the timing of initiation and completion of the 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);
- 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 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 ability to protect our proprietary technology and enforce our intellectual property rights; and

our expectations regarding licensing, acquisitions and strategic operations.

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.

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 triple-action Rhopressa (which we previously referred to as dual-action AR-13324) and quadruple-action Roclatan (which we previously referred to as triple-action PG324), to regulatory approval, and commercialize these products ourselves in the United States. We plan to build a commercial team of approximately 100 sales representatives to target approximately 10,000 high prescribing eye-care professionals throughout the United States. For certain key markets outside the United States, including Europe, Japan and emerging markets, we intend to explore partnership opportunities through collaboration and licensing arrangements. We plan to further maximize our commercial potential by identifying and advancing additional product candidates, both through our internal discovery efforts and through possible in-licensing or acquisitions of additional ophthalmic products or product candidates that would complement our current product portfolio. Our senior leadership team has extensive experience in the ophthalmology market and has overseen the development and commercialization at major pharmaceutical companies of several successful ophthalmic products, including *Acular*, *Alphagan P*, *Bepreve*, *Besivance*, *Bromday*, *Istalol*, *Ocuflox*, *Retisert*, *Vitrase*, *Xibrom* and *Zylet*. If our products are approved and we are commercially successful, we believe Aerie could become a market-leading ophthalmic company.

Our lead product candidate, once-daily, triple-action Rhopressa , completed a Phase 2b clinical trial in patients with open-angle glaucoma and ocular hypertension in May 2013. We are developing Rhopressa as the first of a new class of compounds that is designed to lower intraocular pressure, or IOP, in patients through novel mechanisms of action, or 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 Rhopressa to compete within the prostaglandin analogue, or PGA, market segment due to its equivalent or potentially better efficacy for patients with IOP of 26 millimeters of mercury, or mmHg, or below at the time of diagnosis, which we refer to as low to moderately elevated IOP, while also targeting the diseased tissue responsible for elevated IOP. Approximately 80% of glaucoma patients have low to moderately elevated IOP at the time of diagnosis. Furthermore, we expect Rhopressa to compete against non-PGA products as a preferred add-on therapy to PGAs, due to its strong and consistent IOP-lowering effect with once-daily dosing relative to currently marketed non-PGA products. In addition, we expect Rhopressa to become a preferred therapy where PGAs are contraindicated, for patients who do not respond to PGAs, for patients who have IOPs below 21 mmHg but nevertheless present with glaucomatous damage to the optic nerve, which is commonly referred to as low-tension glaucoma, as well as for patients who choose to avoid the cosmetic issues associated with PGAs. We are currently planning two Phase 3 registration trials for Rhopressa , which we expect to commence in early third quarter 2014 upon completion of Phase 3-enabling toxicology studies.

We are also developing a second product candidate, once-daily, quadruple-action Roclatan , which is a single drop fixed-dose combination of Rhopressa and latanoprost, the most commonly prescribed drug for the treatment of patients with glaucoma. Based on our preclinical data to date, we believe Roclatan has 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 and become the product of choice for patients requiring maximal IOP lowering. In January 2014, we commenced a 28-day Phase 2b clinical trial for Roclatan , for which we expect results in early third quarter 2014.

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Glaucoma is one of the largest segments in the global ophthalmic market. In 2013, branded and generic glaucoma product sales exceeded $4.5 billion in the United States, Europe and Japan in aggregate, according to IMS. Prescription volume for glaucoma products in the United States alone exceeded 31 million in 2013 and is expected to grow, driven in large part by the aging population. The PGA and non-PGA market segments each represent approximately half of the prescription volume in the 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, which results in irreversible vision loss and potentially blindness. Patients may suffer the adverse effects of glaucoma across a wide range of IOP levels, including at normotensive levels between 10 and 21 mmHg, generally accepted as the range of IOP levels in healthy individuals. There are multiple factors that can contribute to an individual getting glaucoma, including 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.

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, while the secondary drainage mechanism, the uveoscleral pathway, is responsible for the remaining drainage. In glaucoma

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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 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.

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) also 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. In addition to our primary product candidates, we are in preclinical development with AR-13533, our second-generation ROCK/NET inhibitor.

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 in glaucoma 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 dosings. 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 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 its 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 initial therapy for patients with low to moderately elevated baseline IOPs of 26 mmHg or below at the time of diagnosis, representing approximately 80% of glaucoma patients. At these IOP levels, we believe the amount of IOP reduction achieved by Rhopressa would be equal to or exceed that of all currently marketed PGA and non-PGA products. In addition, Rhopressa targets the TM, the diseased tissue responsible for elevated IOP in glaucoma and the eye s primary drain, whereas commonly prescribed PGAs and non-PGAs target the secondary drain and the fluid production in the eye, respectively.

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In addition to the expected primary use of Rhopressa as an initial therapy for patients with low to moderately elevated baseline IOPs described above, we also believe Rhopressa may be prescribed by eye-care professionals in the following circumstances:

- 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 to the strong efficacy, more convenient dosing and better tolerability profile of Rhopressa compared to currently marketed non-PGA add-on products. 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 PGA in order to maintain control of IOP.

- As a preferred alternative therapy for patients who do not respond to PGAs.

- As a preferred initial therapy for patients with low-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 IOPs above 26 mmHg and those who present with significant disease progression despite currently available therapies.

We own the worldwide rights to all indications for our current product candidates. We currently plan to commercialize our products ourselves in the United States and to explore partnership opportunities through collaboration and licensing arrangements in certain key markets outside of the United States, including Europe, Japan and emerging markets. In Japan specifically, the Tajimi study found that 90% of glaucoma patients had IOP of 21 mmHg or below at the time of diagnosis, which we believe creates a significant market opportunity in Japan for Rhopressa due to its differentiated ability to reduce IOP at consistent levels across all tested baseline IOPs, as demonstrated in our Phase 2b clinical trial.

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.

Our Product Pipeline

Our primary product candidates, triple-action Rhopressa and quadruple-action Roclatan , are once-daily eye drops. 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 recent

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.

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 1,500 synthesized ROCK-selective and ROCK/NET inhibitors. We continue to seek to

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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 inhibition	Phase 3 registration trials expected to begin early third quarter 2014	Wholly-Owned
Roclatan	Quadruple-action Combination of triple-action Rhopressa and latanoprost, a PGA	Phase 2b clinical trial initiated January 2014	Wholly-Owned
AR-13533	Second-generation ROCK/NET inhibitor	Preclinical	Wholly-Owned

Triple-Action 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. It increases fluid outflow through the primary drain of the eye while also reducing eye fluid production. In addition, a recent 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 cells in the ciliary body of the eye, which reduces the production of eye fluid and thereby lowers IOP.

In addition to its triple MOA, Rhopressa has a number of characteristics that distinguish it from our previously developed product candidates, including ROCK-selective drug AR-12286 and its fixed-dose combination product PG286, and other clinical-stage ROCK inhibitors, which together we refer to as comparator ROCK inhibitors. The active ingredient in Rhopressa , AR-13324, has a unique chemical composition that was specifically designed to allow maximal efficacy of the drug in the eye. Enzymatic conversion of AR-13324 produces two separate molecules, one of which is approximately ten to 160 times more potent at inhibiting ROCK than comparator ROCK inhibitors. This

contributes to greater efficacy and longer duration of effect of AR-13324 relative to comparator ROCK inhibitors that we observed in preclinical models. In addition, AR-13324 has inhibitory activity against a secondary kinase target, Protein Kinase C, or PKC, which is known to act in parallel with ROCK to promote cell contraction. Compounds that inhibit ROCK without inhibiting PKC may allow PKC activity to increase in TM cells over time, resulting in a loss of IOP-lowering efficacy. We believe the ability of

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AR-13324 to inhibit both the primary, ROCK, and secondary, PKC, signaling pathways that lead to TM cell contraction contributes to the ability of Rhopressa to maintain its efficacy over time.

Rhopressa is expected to compete against all products in the glaucoma market, the significant majority of which have been in the market for over 20 years. The PGA and non-PGA market segments each represents approximately 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 its 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 there is a significant unmet need across the glaucoma market due to many drugs requiring multiple daily dosings, side effects and contraindications of other products, and the fact that none of the commonly prescribed drugs target the diseased TM tissue. We believe that triple-action Rhopressa has several significant differentiating characteristics that would make it a strong competitor in both the PGA and non-PGA market segments, if approved, including:

Strong IOP-Lowering Effect In our Phase 2b clinical trial, once-daily Rhopressa demonstrated mean IOP reductions of 5.7 and 6.2 mmHg on days 28 and 14, respectively. Studies have shown that a sustained 5 mmHg reduction in IOP reduces risk of disease progression by approximately 50%. If the results from our Phase 2b trial are confirmed in our planned Phase 3 registration trials, we believe the level of IOP reduction achieved by Rhopressa would be equal to or exceed that of all currently marketed non-PGA products and, in addition, for patients with low to moderately elevated IOPs at the time of diagnosis, representing approximately 80% of glaucoma patients, would be equal to or potentially exceed that of all currently marketed PGA products.

Consistent IOP-Lowering Effect Across Various Baseline IOPs Published studies have indicated that currently marketed PGA and non-PGA products do not lower IOP as effectively in patients with low to moderately elevated baseline IOPs relative to patients with higher IOPs. In our Phase 2b clinical trial, Rhopressa demonstrated a differentiated ability to reduce IOP at consistent levels across all baseline IOPs tested in the trial. The results of a preclinical *in vivo* study sponsored by Aerie and reported in February 2014 suggest that this differentiated effect may be attributable to the ability of Rhopressa to lower EVP.

Novel Triple-Action MOA We believe Rhopressa works through three MOAs: increasing outflow through the TM, decreasing fluid production in the eye and reducing EVP. If approved, we believe Rhopressa would be the only once-daily drug available that works through these three MOAs. In addition, we believe the three MOAs of Rhopressa are highly complementary to the MOA of market-leading PGAs, which increase fluid outflow through the uveoscleral pathway.

Once-Daily Dosing Advantage The most commonly prescribed non-PGA drugs are dosed two to three times daily, which places a considerable daily burden on patients, who are generally required to use these drugs for the remainder of their lives. Rhopressa is being developed as a once-daily dosed glaucoma therapy. This more convenient dosing regimen is expected to result in higher patient compliance, which may lead to improved outcomes.

Favorable Tolerability Profile Currently marketed glaucoma drugs have several tolerability issues indicated on their product labels, including ocular allergic reaction, itching of the eye, iris color change, orbital tissue discoloration, unusual taste and hyperemia. In our Phase 2a and Phase 2b clinical trials for Rhopressa , a total of 209 patients were exposed to Rhopressa . The main tolerability finding for Rhopressa was transient, or temporary, hyperemia, which is a cosmetic asymptomatic redness of the eye. Most of the hyperemia was scored as mild as evaluated by the eye-care professionals in the morning following instillation of the drop the previous night. Hyperemia is a common tolerability finding also associated with PGAs.

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Lack of Systemic Side Effects Rhopressa has demonstrated a lack of systemic side effects in clinical trials to date, including our Phase 1 pharmacokinetic, or PK, study, the results of which were reported in January 2014. Currently marketed non-PGA drugs have systemic side effect issues indicated on their product labels, including among others, lethargy, reduced heart rate, Stevens Johnson syndrome and blood dyscrasias. Furthermore, the most widely prescribed non-PGA drug, timolol, has contraindications that include bronchospasm, arrhythmia and heart failure.

Based on the Phase 2b clinical trial results, and the several positive differentiating attributes of Rhopressa , we believe Rhopressa has the potential to be a strong competitor across the glaucoma market. Our Phase 3 registration trials 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.

Rhopressa™ Phase 2 Efficacy Results

In May 2013, we completed a 28-day Rhopressa Phase 2b clinical trial. This trial included 224 patients who were treated once daily with Rhopressa 0.01%, Rhopressa 0.02% or latanoprost. Latanoprost was used as the comparator because it is the most widely prescribed drug of all currently marketed glaucoma products. The primary efficacy endpoint for this Phase 2b clinical trial was mean diurnal IOP across subjects within each treatment group on day 28. We observed statistically significant decreases in mean diurnal IOP in all treatment groups on day 28 as compared to unmedicated baseline.

Baseline IOP was measured prior to treatment. Following treatment, IOP was measured on day seven at 8 a.m. and on days 14 and 28 at 8 a.m., 10 a.m. and 4 p.m. On day 14, mean diurnal IOP (which refers to the average of mean IOPs measured at 8 a.m., 10 a.m. and 4 p.m.) decreased to 19.8, 19.5 and 18.4 mmHg in the Rhopressa 0.01%, Rhopressa 0.02% and latanoprost groups, respectively, representing a decrease from unmedicated baseline of 5.9, 6.2 and 7.1 mmHg. On day 28, mean diurnal IOP was 20.1, 20.0 and 18.7 mmHg, respectively, representing a decrease from unmedicated baseline of 5.5, 5.7 and 6.8 mmHg. These decreases from unmedicated baseline were statistically significant with p-values < 0.001. P-value, or probability value, is a statistical measure that helps scientists determine if their hypotheses are correct. It is directly related to the statistical significance level of the results, which is an important component in determining whether the data obtained from scientific research support the hypothesis being tested.

The statistical significance level is determined by the researcher and is customarily set at 0.05, or 5%. Essentially, this means that 5% of the time, the results in the study would be derived by complete chance, but 95% of the time, the variable in the study would be directly related to the results of the study. Efficacy results from the Phase 2b trial are further described below.

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Efficacy Results of the 28-day Phase 2b Clinical Trial Comparing Rhopressa™ to Latanoprost

Showing Mean Diurnal IOP for Days 14 and 28 Compared to Baseline

Rhopressa maintained consistent efficacy from day seven to day 28. For Rhopressa 0.02%, which is the concentration we intend to use in our planned Phase 3 trials, at the 8 a.m. time point, the time of highest baseline IOP, the IOP reductions achieved on day seven and day 28 were 6.0 and 5.9 mmHg, respectively. The level of IOP reduction achieved by Rhopressa 0.02% in our Phase 2b study was clinically significant, since previously published long-term studies have demonstrated that a sustained 5 mmHg reduction in IOP reduces the risk of disease progression by approximately 50%.

Clinical significance means that the effect is large enough to be important to patients and physicians. An effect that is statistically significant may or may not also be clinically significant. In glaucoma, the Early Manifest Glaucoma Trial, a large long-term study evaluating the effect of IOP lowering in patients with glaucoma, concluded that each 1 mmHg reduction in IOP lowered the risk of progression of optic nerve damage by 10%, indicating that each 1 mmHg reduction in IOP provides a meaningful level of protection to the patient.

IOP-Lowering Effect of Rhopressa™ 0.02% at 8 a.m. on Days 7, 14 and 28

In the full Phase 2b trial population, which consisted of patients with unmedicated baseline IOPs ranging from 22 to 36 mmHg, the IOP-lowering effect of our once-daily Rhopressa 0.02% was 1.2 mmHg less than that of latanoprost on day 28 and did not show non-inferiority. However, Rhopressa 0.02% efficacy relative to

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latanoprost was in line with published historical data for twice-daily timolol relative to latanoprost. Timolol is the most commonly prescribed non-PGA drug and the comparator for our planned Phase 3 non-inferiority registration trials.

A study by Hedman and Alm, which reports on the pooled data from three registration trials of latanoprost versus timolol, showed the IOP-lowering effect of timolol to be 1.2 mmHg less than that of latanoprost, as reflected in the graph on the following page under the heading Comparison of Latanoprost and Timolol from Pooled Data of Three Registration Trials. Our Rhopressa Phase 2b clinical trials similarly showed Rhopressa to have an IOP-lowering effect of 1.2 mmHg less than that of latanoprost.

An additional protocol-specified analysis that compared the results for the patients who entered the trial with moderately elevated baseline IOPs (22 to 26 mmHg) to patients with highly elevated baseline IOPs (greater than 26 mmHg) revealed a differentiated efficacy profile of Rhopressa compared to latanoprost. Consistent with previous scientific literature, latanoprost produced smaller IOP reductions in patients with moderately elevated IOPs than in patients with highly elevated IOPs. In contrast, Rhopressa maintained essentially the same IOP-lowering effect in patients with moderately elevated IOPs as in patients with highly elevated IOPs ($p>0.30$). As a result, the IOP-lowering effect of Rhopressa was equivalent to latanoprost in patients with moderately elevated baseline IOPs and Rhopressa thereby demonstrated statistical non-inferiority to latanoprost in this sub-group. A non-inferiority trial is a type of clinical trial performed to see if a new drug or treatment is *not inferior* to a current active treatment or to determine if a new treatment is *at least as good as,* or *not unacceptably worse than*, the active comparator treatment. A non-inferiority trial aims at demonstrating that the test product is not worse than the comparator by more than a small pre-specified amount. This amount is known as the non-inferiority margin, which for the Rhopressa Phase 2b trial was 1.5 mmHg.

IOP-Lowering Effect of Rhopressa™ 0.02% and Latanoprost in the Full Patient Population

Compared to the Subgroup with Moderately Elevated IOP*

* Based on diurnal measurements.

A study published in 2000, which pooled data from three latanoprost registration trials, demonstrated that both latanoprost and timolol lose approximately 0.5 mmHg in efficacy for every 1 mmHg lower baseline IOP, as illustrated in the chart below. Additional publications have indicated similar declining efficacy results for other currently marketed non-PGA glaucoma drugs, including the alpha agonist brimonidine and the carbonic anhydrase inhibitor dorzolamide.

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Comparison of Latanoprost and Timolol from Pooled Data of Three Registration Trials

Source: Hedman and Alm (Eur J Ophthalmol 2000; 10:95-104)

We believe the ability of Rhopressa to maintain a consistent IOP-lowering effect on baseline IOP will place Rhopressa in a favorable competitive position relative to current PGA and non-PGA products because a significant majority of glaucoma patients have baseline IOPs of 26 mmHg or below at the time of diagnosis. Results from a large epidemiological survey published in 1991, the Baltimore Eye Survey, demonstrated that greater than 78% of patients have unmedicated baseline IOPs of 26 mmHg or below when first diagnosed with glaucoma.

Prevalence of Glaucoma by Baseline IOP at the Time of Diagnosis

Adapted from Baltimore Eye Survey in which 10,444 subjects were screened for the prevalence of Open-Angle Glaucoma (OAG)

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Furthermore, in the Tajimi Study carried out in Japan in 2000 and 2001, 92% of patients with primary open-angle glaucoma were found to have IOPs of 21 mmHg or less at the time of diagnosis. In this study, 3,870 randomly selected residents of the city of Tajimi were screened for primary open-angle glaucoma.

Rhopressa™ Phase 2a Efficacy Results

In August 2012, we completed a 7-day Rhopressa Phase 2a clinical trial. This trial included 85 patients who were treated once-daily with Rhopressa 0.01%, Rhopressa 0.02%, Rhopressa 0.04% or the vehicle of Rhopressa . Vehicle refers to the formulation without the active ingredient. Baseline IOP was measured prior to treatment. IOP was measured following seven days of dosing at 8 a.m., 10 a.m., 12 p.m. and 4 p.m. The primary efficacy endpoint for this Phase 2a clinical trial was the mean diurnal IOP (which refers to the average of mean IOPs measured at 8 a.m., 10 a.m., 12 p.m. and 4 p.m.) across subjects within each treatment group on day eight. We observed statistically significant decreases in mean diurnal IOP in all Rhopressa treatment groups following seven days of dosing compared to unmedicated baseline. Additionally, each concentration of Rhopressa was shown to be statistically superior to the vehicle following seven days of dosing with p-values ranging from 0.018 to <0.001.

Rhopressa™ Phase 2 Safety Data

In our 7-day Phase 2a and 28-day Phase 2b clinical trials for Rhopressa a total of 209 patients were exposed to Rhopressa . In these trials, Rhopressa was well tolerated. The main adverse event was transient hyperemia, or asymptomatic redness of the eye, with all hyperemia scored as mild or moderate. This cosmetic tolerability finding is based on the MOA of the drug, which induces a transient dilation of small blood vessels located over the sclera, or white part of the eye.

The biomicroscopy findings in the Phase 2b trial for the vast majority of patients who experienced ocular hyperemia were mild and transient, and there were no observations of severe ocular hyperemia. Biomicroscopy refers to the observation by a masked examiner of the anterior part of the eye. On day 28 at 8 a.m., mild and moderate conjunctival hyperemia was observed in 18% and 24% of patients in the Rhopressa 0.01% and 0.02% treatment groups, respectively, and in 11% of patients in the latanoprost group. The incidence of conjunctival hyperemia decreased throughout the study for Rhopressa and increased for latanoprost.

Published data indicate that latanoprost generates the lowest rate of hyperemia among the commonly prescribed PGAs. In a study that compared the relative frequency of hyperemia for bimatoprost, travaprost and latanoprost after 12 weeks of treatment, the largest proportion of patients reporting redness was found in the bimatoprost group with 35%, followed by the travoprost and latanoprost groups with 27% and 16%, respectively.

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Rhopressa™ Comparison to AR-12286

We have analyzed our clinical and preclinical data for Rhopressa , the lead candidate from our ROCK/NET inhibitor class, relative to our clinical and preclinical data for AR-12286, our ROCK-selective compound that we were previously evaluating for further clinical development in addition to Rhopressa . We conducted similarly designed 28-day Phase 2 clinical trials for each of Rhopressa and AR-12286, the comparative results of which are presented in the chart below. Rhopressa 0.02% maintained stable efficacy on day 28 relative to day seven in its 28-day Phase 2 clinical trial. In contrast, AR-12286 0.5% lost 1.4 mmHg of IOP-lowering efficacy from day seven to day 28 in its 28-day Phase 2 clinical trial.

IOP-Lowering Effect of Rhopressa™ and AR-12286

at 8 a.m. on Days 7, 14 and 28

We subsequently completed a three-month Phase 2 clinical trial for AR-12286, for which data were available in June 2013. This trial confirmed the trend observed in the 28-day trial discussed above. In the three-month trial, the efficacy of AR-12286 continued to decline over the trial period such that it failed to meet its primary efficacy endpoint, non-inferiority to timolol.

Our lead product candidate, Rhopressa , has a number of characteristics that distinguish it from AR-12286. Rhopressa lowers IOP by inhibiting both ROCK and NET, whereas AR-12286 inhibits only ROCK. In addition, the active ingredient in Rhopressa , AR-13324, has a unique chemical composition that was specifically designed to allow maximal efficacy of the drug in the eye. Enzymatic conversion of AR-13324 produces two separate molecules, one of which is approximately ten times more potent at inhibiting ROCK than AR-12286. The more potent ROCK inhibition provided by Rhopressa , as well as its ability to inhibit NET, contributes to its greater efficacy and longer duration of effect relative to AR-12286.

In addition, the analyses of our data suggest that there is a secondary signaling pathway that is activated by a protein called PKC that also leads to contraction of the TM. Our preclinical analyses show that AR-13324 is a potent inhibitor of both ROCK and PKC, whereas AR-12286 is a potent inhibitor of ROCK but not of PKC. We believe that the ability of AR-13324 to inhibit both the primary, ROCK, and the secondary, PKC, signaling pathways that lead to TM cell contraction contributes to the ability of Rhopressa to maintain its efficacy over time.

Furthermore, in a six-month toxicology study with exaggerated dosing of AR-12286, lens opacities, otherwise known as cataracts, were observed in rabbit eyes beginning at three months. In a similar six-month toxicology study with exaggerated dosing of Rhopressa , no adverse lens effects were observed.

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As a result of these observations, in June 2013, we selected Rhopressa for advancement to Phase 3 clinical development and discontinued development of AR-12286 and its related fixed-dose combination product PG286.

Rhopressa™ Phase 1 Pharmacokinetic Study Results

In January 2014, we reported top-line results from our recently completed Phase 1 PK study, in which Rhopressa eye drops were administered once daily to 18 healthy individuals over an eight-day period to assess systemic exposure to the drug. In addition, the drug s effect on IOP was measured. All study subjects had normotensive IOPs in the range of 12 to 21 mmHg, with an average diurnal IOP for the group of approximately 16 mmHg prior to dosing. The PK study demonstrated very low systemic exposure to Rhopressa , with blood levels at or below the limit of detection of 0.1 ng/mL at all time points, and no drug-related effects on systemic safety parameters such as blood pressure and heart rate. Of particular importance to the product s efficacy profile, the subjects average diurnal IOP decreased by approximately 5 mmHg, or more than 30%, to approximately 11 mmHg after the eight days of dosing. The completion of the PK study is an important step in preparing for our two planned Phase 3 registration trials of Rhopressa , which are expected to begin in early third quarter 2014.

Rhopressa™ Preclinical in Vivo Study Results

We believe that the strong IOP-lowering effect of Rhopressa at lower baseline IOPs, and its consistent IOP-lowering effect across all tested baseline IOPs, are due in part to the ability of Rhopressa to lower EVP, which accounts for approximately half of IOP in normotensive individuals. This is an MOA that we believe further differentiates Rhopressa from currently marketed PGA and non-PGA products. The EVP-lowering effect of Rhopressa was demonstrated in a preclinical *in vivo* rabbit study sponsored by Aerie, the results of which we reported in February 2014. In this study, Rhopressa demonstrated statistically significant reductions in EVP and IOP following the third daily dose. EVP decreased by 35% relative to baseline, and IOP was reduced by 39%. Based on these study results, it was estimated that up to 42% of the reduction in IOP caused by Rhopressa was due to the reduction in EVP.

Rhopressa™ Development Strategy

Registration trials for Rhopressa are expected to begin in early third quarter 2014 upon completion of three-month interim study reports from our six-month and nine-month Phase 3-enabling ocular toxicology studies. The Rhopressa doses and dosing frequencies being tested in these studies have previously been shown to be well tolerated in 28-day and six-month ocular toxicology studies. We plan to run two pivotal trials that will include at least 1,200 patients in total. The entry criteria for our Phase 3 trials are planned to include a minimum IOP of 21 mmHg and a maximum of 26 mmHg. Based on discussions with the FDA, we believe that the planned entry criteria for our Phase 3 trials are acceptable to the FDA and will not impact the product label. The entry criteria for our Phase 2 trials were 22 to 36 mmHg. Lowering the IOP entry criteria for our Phase 3 trials will increase the representation of patients with moderately elevated IOPs in the trials and thereby provide a more representative cross-section of the glaucoma patient population. The registration trials will be non-inferiority trials comparing Rhopressa 0.02% taken once daily in the evening to twice-daily timolol, the standard comparator for glaucoma registration trials and also the most widely prescribed non-PGA glaucoma drug. Phase 3 efficacy results will be determined after three months of treatment and safety results will be analyzed and submitted following 12 months of treatment. Assuming we commence the Phase 3 trials in early third quarter 2014 and fully enroll the trials within our anticipated timeframe, we would expect efficacy data from the two trials in mid-2015 and, if the results of the Phase 3 trials are positive, that we would make a new drug application, or an NDA, filing by mid-2016. We intend to explore the potential for priority review with the FDA, although there can be no assurance that such priority review will be granted by the FDA.

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Quadruple-Action 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.

Quadruple-action Roclatan has been tested in a preclinical primate model to assess its effectiveness at lowering IOP. The graph below presents the data from dosing Roclatan and latanoprost once daily for three days (at hours 0, 24 and 48). The results of the study show that at all time points measured, Roclatan reduced IOP substantially more than latanoprost alone. No IOP measurements were taken on day two of the study between hours 24 and 48.

* SEM refers to Standard Error of the Mean.

In addition, we have established human proof of concept in prior ROCK inhibitor/PGA combination trials with our discontinued PG286 product, which demonstrated significant IOP lowering beyond the PGA alone at 28 days.

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 IOPs above 26 mmHg and those who present with significant disease progression despite currently available therapies.

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Roclatan™ Development Strategy

In light of the clinical experience with Rhopressa to date and the extensive clinical experience with latanoprost, which has been used in patients for approximately 20 years, we advanced Roclatan directly into a Phase 2b clinical trial in January 2014. Roclatan is covered by the investigational new drug application, or IND, for Rhopressa . We have 28-day toxicology data to support a 28-day clinical trial. The process followed for the Phase 2b clinical trial is consistent with normal FDA guidelines, including the submission of the protocol to the FDA. The trial is a randomized, controlled 28-day trial in approximately 300 patients. The trial is designed to measure the efficacy of two concentrations of Roclatan (with AR-13324 0.01% or 0.02% concentrations) compared to latanoprost and Rhopressa 0.02%, all dosed once daily. The efficacy endpoint is superiority of Roclatan to each of its components. We expect the results of this Phase 2b trial in early third quarter 2014. The Phase 3 registration trial for Roclatan is expected to mirror the Phase 2b trial but with three-month efficacy and a 12-month safety trial, and will only test one concentration of Roclatan .

Second-Generation AR-13533

In addition to our primary product candidates, Rhopressa and Roclatan , we are in the preclinical development stage with AR-13533, our second-generation ROCK/NET inhibitor. AR-13533 does not require enzymatic conversion in the eye to deliver maximal ROCK inhibitor activity, and therefore AR-13533 may provide additional IOP-lowering effect in patients beyond that obtained with Rhopressa . We have not submitted an IND for AR-13533 to the FDA and there can be no assurance that an IND will be submitted.

Our Strategy

Our goal is to be 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. Based on the results from our Phase 2b clinical trial for triple-action Rhopressa , we plan to proceed into Phase 3 registration trials for this drug in early third quarter 2014. In January 2014, we initiated a Phase 2b clinical trial for Roclatan , our quadruple-action combination of Rhopressa and latanoprost and, over the longer term, we plan to evaluate opportunities associated with preclinical-stage AR-13533, our second-generation ROCK/NET inhibitor.

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

Explore partnerships with leading pharmaceutical and biotechnology companies to maximize the value of our product candidates outside the United States. We currently plan to explore the licensing of commercialization rights or other forms of collaboration with qualified potential partners for the commercialization of our product candidates in certain key markets outside of the United States, including Europe, Japan and emerging markets.

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. 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.

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Expand our product portfolio through internal discovery efforts and possible 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 evaluate the expansion of our product portfolio through in-licensing or acquisitions of additional ophthalmic product candidates or products.

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 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 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.

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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 Bausch + Lomb, Inc. (acquired in 2013 by Valeant Pharmaceuticals International, Inc.), Merck & Co., 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 to treat glaucoma. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that the key competitive factors affecting the success of our product candidates, if approved, are likely to be efficacy, safety, convenience, price, tolerability and the availability of 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 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

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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