# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208254Orig1s000

# SUMMARY REVIEW

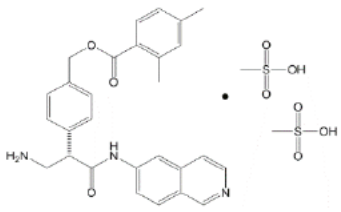
# Cross-Discipline Team Leader, Deputy Division Director (DTOP), and Deputy Office Director (OAP) Summary Review of NDA 208254

| | |
|---|---|
| **Date** | December 1, 2017 |
| **From** | William M. Boyd, M.D., Wiley A. Chambers, M.D., and John Farley, M.D. |
| **Subject** | Cross-Discipline Team Leader Review and Action Summary Review |
| **NDA/BLA # and Supplement#** | NDA 208254 |
| **Applicant** | Aerie Therapeutics, Inc. |
| **Date of Submission** | 2/28/2017 |
| **PDUFA Goal Date** | 2/28/2018 |
| **Proprietary Name** | Rhopressa |
| **Established or Proper Name** | netarsudil ophthalmic solution, 0.02% |
| **Dosage Form(s)** | ophthalmic solution |
| **Proposed Indication(s)/Population(s)** | reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension |
| **Proposed Dosing Regimen(s)** | one drop into the affected eye(s) once daily in the evening |
| **Regulatory Action** | Approval |

## 1. Benefit-Risk Assessment

Netarsudil is a Rho kinase inhibitor. Rho kinase (ROCK) inhibitors represent a new class of medications that lower IOP and netarsudil is a NME (new molecular entity). The established name is netarsudil ophthalmic solution and the proposed proprietary name is Rhopressa, 0.02%. During development, the product was also referred to as AR-13324.

Its chemical name is (S)-4-(3-amino-1 (isoquinolin-6-yl-amino)-1-oxopropan-2-yl)benzyl 2,4-dimethylbenzoate dimesylate. Its molecular formula is $C_{30}H_{35}N_3O_9S_2$ and its chemical structure is:



Netarsudil mesylate is a light yellow to white powder that is freely soluble in water, soluble in methanol, sparingly soluble in dimethyl formamide, and practically insoluble in dichloromethane and heptane.

Age Groups: patients 18 years or older

**Benefit-Risk Assessment Framework**

**Benefit-Risk Integrated Assessment**

The data contained in this submission establishes the efficacy of netarsudil ophthalmic solution, 0.02% dosed once daily in the evening for lowering elevated IOP in patients with open-angle glaucoma or ocular hypertension. Elevated IOP is a major risk factor in the development of visual field loss in patients with open-angle glaucoma.

Studies 301, 302, and 304 demonstrate that the IOP lowering ability of netarsudil ophthalmic solution 0.02% in the subgroup of patients with baseline intraocular pressures of <25 mmHg is equivalent to timolol maleate ophthalmic solution, 0.5%.

The most common ocular adverse events for netarsudil are: conjunctival hyperemia, corneal verticillata, conjunctival hemorrhage, and instillation site pain. To date, no long term consequences of netarsudil administration have been identified.

The potential benefits of netarsudil ophthalmic solution, 0.02% through lowering elevated IOP in patients with open-angle glaucoma or ocular hypertension outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors for the development of glaucoma is elevated IOP. | Intraocular pressure is currently the only modifiable risk factor for minimizing the chances of visual field loss due to glaucoma. |
| Current Treatment Options | • There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues. It is not uncommon for a patient with glaucoma to require more than one class of IOP lowering products to control elevated IOP. | This product, if approved, would provide availability of a product in a new class to lower intraocular pressure. It is expected that many patients will need more than one class of IOP lowering products. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Benefit** | • IOP is currently the accepted standard for measuring the efficacy of ocular hypotensive medications. The primary efficacy endpoint was the mean IOP measured at multiple time points for studies 301, 302, and 304. These studies demonstrated that in the subset of patients with IOP <25, netarsudil ophthalmic solution, 0.02% was equivalent to a known effective product. | Studies 301, 302, and 304 demonstrated that in the subset of patients with IOP <25 mmHg, netarsudil ophthalmic solution, 0.02% was equivalent to timolol maleate ophthalmic solution, 0.5%, a product known to be effective in lowering IOP. |
| **Risk** | • Rho kinase (ROCK) inhibitors represent a new class of medications that lower IOP. The risks observed in the clinical trials were a high frequency of conjunctival hyperemia and the formation of corneal verticillata. Other risks may emerge for this new class during routine post-market safety surveillance. | The safety database contained in this application identified potential adverse events which may be expected to occur at rates of 1% or greater following the use of netarsudil ophthalmic solution, 0.02% dosed once daily in the evening. |

# 2. Background

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. Glaucoma affects one person in 200 over the age of 40 and is the leading cause of irreversible blindness in the United States. One of the primary risk factors is elevated IOP. The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy. There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs. When maximal tolerated medical therapy does not adequately control IOP, surgical therapy (with its associated risks) is the next option.

**Summary of Pre-submission/Submission Regulatory Activity**

| | |
|---|---|
| Pre-Investigational New Drug 113064 telephone conference | 10/31/11 |
| End of Phase 2 meeting | 4/11/14 |
| Type C guidance telephone conference | 6/12/15 |
| Chemistry/Manufacturing Controls telephone conference | 12/17/15 |

NDA Mid-Cycle Communication 7/27/17

Significant review issues relayed to applicant:

- The IOP reduction with Rhopressa 0.02% dosed once daily was not non-inferior to the effect of timolol 0.5% dosed twice daily over the range of IOPs for which timolol is effective.
- Bilateral cornea verticillata/ corneal opacities noted after onset of treatment.

NDA Late-Cycle Communication 9/29/17

Significant issues relayed to applicant:

- The IOP reduction with Rhopressa 0.02% dosed once daily was not non-inferior to the effect of timolol 0.5% dosed twice daily over the range of IOPs for which timolol is effective.
- Bilateral cornea verticillata/ corneal opacities noted after onset of treatment.

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting 10/13/17

# 3. Product Quality

See the Product Quality review finalized 10/30/2017.

**DRUG SUBSTANCE**

## Netarsudil Mesylate Drug Substance Specification

| Test | Acceptance Criteria | Analytical Procedure |
|---|---|---|
| Description | Light yellow to white powder. | Visual (AD017 TST) |
| Identification of AR-13324<br>IR[1]<br>HPLC[1] | Conforms to reference standard spectrum.<br>The retention time of the main peak in the sample chromatogram corresponds to that of the main peak in the standard chromatograms. | FTIR (USP <197>; AD002 TST)<br>HPLC (AD130 TST) |
| Assay (anhydrous basis, % w/w) | (b) (4) | HPLC (AD130 TST) |
| Chromatographic Purity (% w/w)[2]<br>(b) (4)<br>Total Impurities[3] | | HPLC (AD130 TST) |
| (b) (4) | | HPLC (AD072 TST) |
| | | IC (AD121 TST) |
| | | GC-HS (AD082 TST) |
| Residual Solvents (ppm)[1]<br>(b) (4) | | GC-HS (AD137 TST)<br>GC (AD142 TST) |
| Water Content (% w/w) | | Karl Fischer (USP <921>; AD004 TST) |
| Elemental Impurities (µg/g)[1]<br>(b) (4) | | ICP-MS (USP <233>, <232>; AD077 TST) |

| Test | Acceptance Criteria | Analytical Procedure |
|---|---|---|
| Microbial Bioburden Test<br>Total Aerobic Count<br>Total Yeasts & Mold Count<br>Absence of objectionable organisms[4] | (b) (4) | Microbiological Examination (USP <61>, <62>; AD050 TST) |
| (b) (4) | | HPLC (AD073 TST) |
| | | GC (AD106 TST) |
| Residue on Ignition (% w/w)[1,5] | | (USP <281>; AD114 TST) |

NMT = Not More Than; CFU = Colony Forming Units

1 (b) (4)

2 Structures and names of impurities are provided in Section 3.2.S.3.2.

3 Total Impurities includes all impurities observed at or above (b) (4)% in the chromatographic purity test. (b) (4) is not included in the Total Impurities.

4 Objectionable organisms: *Staphylococcus aureus; Pseudomonas aeruginosa; Bacillus subtilis; Candida albicans; Aspergillus brasiliensis; Escherichia coli; Salmonella enterica; Burkholderia cepacia.*

5 As proposed in the Type B Pre-NDA CMC Meeting IND 113064 Serial Number 0088 these tests will (b) (4)

see Section 3.2.S.4.5.

From Module 3.2.S.4.1

**DRUG PRODUCT**

**Composition and Components of Netarsudil Ophthalmic Solution 0.02%**

| | | Netarsudil Concentration: 0.2 mg/mL | |
|---|---|---|---|
| | | per mL (mg) | Quantity (% w/v) |
| Netarsudil mesylate | Active Ingredient | 0.2 (b) (4) | 0.02 |
| Mannitol | (b) (4) | | |
| Boric acid | | | |
| Benzalkonium chloride | Preservative | (b) (4) | 0.015 |
| Sodium hydroxide[3] | pH Adjuster | as needed | as needed |
| Water for Injection | (b) (4) | | |
| **Total** | | 1 mL | 100% |

(b) (4)

From Module 3.2.P.1

**Specifications for Netarsudil Ophthalmic Solution 0.02% Drug Product**

| Test | Acceptance Criteria |
|---|---|
| Description | Clear solution, free of visible particles |
| pH | 4.2 – 5.2 |
| Osmolality (mOsm/kg) | 250 – 340 |
| Identification of AR-13324 by UV[1] | UV Spectrum of sample is essentially the same as that of AR-13324 reference standard |
| Identification of AR-13324 by Retention Time[1] | The retention time of the main peak in the sample corresponds to that of the AR-13324 reference standard |
| Assay: AR-13324 content (% LC) | (b) (4) |
| (b) (4)<br>Any unspecified degradation product<br>Total degradation products[3] | |
| (b) (4) content (% w/w) | |
| Benzalkonium Chloride (% LC) | |
| Particulate Matter | Meets requirement of USP<789><br>NMT 50 particles/mL ≥10 µm NMT 5 particles/mL ≥25 µm NMT 2 particles/mL ≥50 µm |
| Sterility | Meets requirements of USP <71> |
| Antimicrobial Effectiveness Test[4] | Meets Requirements of USP <51> for Category 1 product |

UV = Ultraviolet detection LC = Label Claim NMT = Not More Than NLT = Not Less Than

1
2
3
4 (b) (4)

From Module 3.2.P.5.1

**FACILITY INSPECTIONS**

| Establishment Name and Address | FEI Number | Responsibilities and profile codes | Initial Assessment | Final Recommendation |
|---|---|---|---|---|
| (b) (4) | | DS manufacturing, release test and stability test, (b) (4) | • Low | • Acceptable based on inspection history and manufacturing capacity |
| | | DS release test | Low | Acceptable based on the firm's inspection history and manufacturing capability |
| | | DS release test | Low | Accetable based on the firm's inspection history and manufacturing capability |
| | | DS release test | Low | AC based on the firm's inspection history and manufacturing capability |

These drug substance sites were all found to be acceptable. For detailed reviewer comments, see the Product Quality review finalized 10/30/17.

| Establishment Name and Address | FEI Number | Responsibilities and profile codes | Initial Assessment | Final Recommendation |
|---|---|---|---|---|
| (b) (4) | | DP manufacturing, stability test and release test, (b) (4) | • OAI in (b) (4) | • Acceptable based on PAI findings, Approve based on RAI response and tcon with sponsor/manufacturing facility. |
| | | DP release test and stability test, CTL | Low | Acceptable based on the firm's inspection history and manufacturing capability |

These drug product sites were all found to be accptable. For detailed reviewer comments, see the Product Quality review finalized 10/30/17.

[redacted]

On [redacted] the firm submitted application for Rhopressa (netarsudil ophthalmic solution) 0.02% stating that the issues observed during the last inspection of the facility were the drug product will be manufactured were resolved. Product review and process review are both adequate for this submission. To verify whether all the corrective actions were implemented by the firm, a PAI was conducted on [redacted] Rhopressa is one of the pre-approval applications covered during the inspection in [redacted]

During the inspection, corrective actions were verified and found adequate except for the corrective actions to the [redacted] deficiency. In addition, 10 more deficiencies were found during this PAI including a [redacted]

This inspection was initially classied OAI. However, based on the response received from the firm, ORA recommended that the inspection be reclassified to VAI with an expedited re-inspection. OPF concurs with this assessment. The facility is now considered acceptable for this NDA. However, an expedited post-approval inspection is recommended to verify the firm's corrective actions. ORA is also recommending an expedited re-inspection.

**SUMMARY**

Satisfactory information and response have been submitted to support the quality of the drug substance, drug product, process and quality micro aspects. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 10-27-2017. Therefore, NDA 208254 is recommended for approval from Product Quality perspective.

## 4. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology revew in DARRTS dated 11/6/2017.

The ocular safety of Netarsudil Ophthalmic Solution was evaluated in rabbits and monkeys in repeat-dose ocular toxicity studies of 7-day, 28-day, 3/6-month (rabbits) and 9-month (monkey) duration. Findings in both species included signs of ocular irritation, (i.e., conjunctival congestion [hyperemia], discharge and/or swelling), corneal alterations (haze, opacities, peripheral vascularization, mixed cell inflammation, attenuation of the overlying corneal epithelium, punctate ulcers, hypertrophy/hyperplasia, edema, and/or apoptosis), and decreased IOP (intended pharmacological effect). The severity and extent of these findings was dose dependent.

Generally, the signs of ocular irritation and corneal alterations decreased in severity or resolved despite continuous dosing, or resolved during the recovery period. Exposure margins were 8-fold (monkey) and 2-fold (rabbit) at the intended clinical dose regimen, based on the NOAEL from the chronic ocular toxicity studies.

The NOEL for corneal haze provides an exposure margin of 1 at the intended clinical dose. Netarsudil is a cationic amphiphilic drug, which are known to induce phospholipidosis. Netarsudil induced phospholipidosis in a cell-based assay. As noted by the applicant, it is possible that the finding of corneal haze in monkeys is related to the findings of "corneal deposits" and "corneal verticillata" associated with Netarsudil Ophthalmic Solution 0.02% treatment in Phase 3 clinical studies.

The systemic toxicity profile of netarsudil was evaluated in rats and dogs in repeat dose studies of 7-day and 28-day duration by the intravenous route. Based on the results of the systemic toxicity studies in rats and dogs, as well as the cardiovascular safety pharmacology study in telemetered dogs, common findings included cardiovascular (decreased blood pressure, increased heart rate) effects and inflammation at the site of injection. The vasodilation is an expected pharmacological effect of Rho-kinase inhibitors.

Additional targets observed at the highest doses tested in the early short-term (7-day) repeat-dose IV toxicity studies in rats and/or dogs included the hematopoietic system (RBC parameters and WBC types alterations, bone marrow and lymph nodes microscopic findings), blood coagulation system (increased PT and/or APTT) and several organs (microscopic findings in the heart, kidneys, lungs, gallbladder, urinary bladder and thymus). Based on the observed clinical exposure of netarsudil generally below the lower limit of quantitation of 0.100 ng/mL at the recommended clinical dose, it is unlikely these findings are clinically relevant.

Embryofetal development toxicity studies in both rats and rabbits showed dose dependent increases in parameters associated with toxicity to the embryo and fetus such as increased early resorptions, increased in post-implantation loss, decreases in litter size, decreased number of mothers with viable fetuses, and decreased number of viable fetuses.

Signs indicative of abortions were observed in rats. Offspring anomalies were limited to a slight increase in the mean number of ossified caudal vertebrae at ≥0.1 mg/kg/day and forelimb phalanges at ≥0.03 mg/kg/day.

The applicant concluded that there were no AR-13324-related fetal external, soft tissue, or skeletal fetal malformations or variations at any dose in rabbits. However, there were some findings with higher incidence in test-article treated groups. These included umbilical hernia and thoracogastroschisis in one high-dose (5.0 mg/kg/day) and one middose (3.0 mg/kg/day) fetus, respectively, and increased number of fetuses with absent intermediate lung lobe at 5.0 mg/kg/day. Although the umbilical hernia and thoracogastroschisis were observed in one fetus each, these are rare findings. In addition, the incidence was above the historical control range (Charles River Historical Control database, June 2008-2010).

The exposure margins at the NOAEL for embryofetal development toxicity were >40-fold (rat) and >1300-fold (rabbit). Based on the observed clinical exposure of netarsudil generally below the lower limit of quantitation of 0.100 ng/mL at the recommended clinical dose, there is low risk for embryofetal toxicity to be observed at the intended dosing regimen.

Netarsudil did not show mutagenic or clastogenic potential in the full battery of genetic toxicity studies conducted. Carcinogenicity studies were not conducted. The justification provided by the applicant to omit these studies was considered acceptable.

In conclusion, the nonclinical data presented in this NDA provides adequate safety support for the intended dosing regimen of Netarsudil Ophthalmic Solution 0.02% once daily ( (b) (4) mg/eye) for the indication of reduction of IOP. Approval is recommended from the nonclinical perspective.

# 5. Clinical Pharmacology

See the Clinical Pharmacology review in DARRTS dated 8/30/2017.

The Phase 1 study AR-13324-CS101 is a pharmacokinetic study conducted in healthy subjects to assess the tolerability and safety of netarsudil ophthalmic solution, 0.02%, as well as the systemic exposure of netarsudil and the primary active metabolite AR-13503. The clinical PK study demonstrated that the systemic exposures of netarsudil and the active metabolite are negligible following repeat topical ocular application of netarsudil ophthalmic solution, 0.02%.

The Clinical Pharmacology information provided by the Applicant in the NDA submission was found to be acceptable, and the Clinical Pharmacology review team recommends approval of Rhopressa (netarsudil ophthalmic solution) 0.02%.

# 6. Clinical Microbiology

Not applicable. This product is not an anti-infective.

# 7. Clinical/Statistical - Efficacy

Although all submitted studies were reviewed, the primary support for efficacy is from three clinical studies (Studies AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304). These trials went under the acronym, "Rho Kinase Elevated Intraocular Pressure Treatment Trial" or "Rocket." See the Medical Officer's review in DARRTS dated 11/8/2017.

| Study Name | Study Design | Test product | Number of Subjects | Healthy Subjects or Diagnosis of Subjects | Duration of Treatment | Study Status |
|---|---|---|---|---|---|---|
| AR-13324-CS301 | Double-masked, randomized, multi-center, active controlled, parallel study | Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM<br><br>Netarsudil ophthalmic solution placebo 1 gtt OU QAM<br><br>Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID | 411 | Subjects with elevated IOP | 3 months | Complete |
| AR-13324-CS302 | Double-masked, randomized, multi-center, active controlled, parallel study | Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM<br><br>Netarsudil ophthalmic solution Placebo 1 gtt OU QAM<br><br>Netarsudil ophthalmic solution 0.02% 1 gtt OU BID<br><br>Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID | 756 | Subjects with elevated IOP | 12 months | Complete |

| Study Name | Study Design | Test product | Number of Subjects | Healthy Subjects or Diagnosis of Subjects | Duration of Treatment | Study Status |
|---|---|---|---|---|---|---|
| AR-13324-CS304 | Double-masked, randomized, multi-center, active controlled, parallel study | Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM<br><br>Netarsudil ophthalmic solution placebo 1 gtt OU QD AM<br><br>Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID | 708 | Subjects with elevated IOP | 6 months | Complete |

**Study AR-13324-CS301: A double-masked, randomized, multi-center, active controlled, parallel, 3-month study assessing the safety and ocular hypotensive efficacy of AR-13324 ophthalmic solution, 0.02% compared to timolol maleate ophthalmic solution, 0.5% in patients with elevated intraocular pressure**

For adult subjects, the primary efficacy outcome was to be the mean IOP at 08:00, 10:00, and 16:00 hours at the Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90) visits. Separate analysis populations were to be defined for subjects 0 to 2 years old and for subjects 18 years of age and older; however, no pediatric subjects were enrolled.

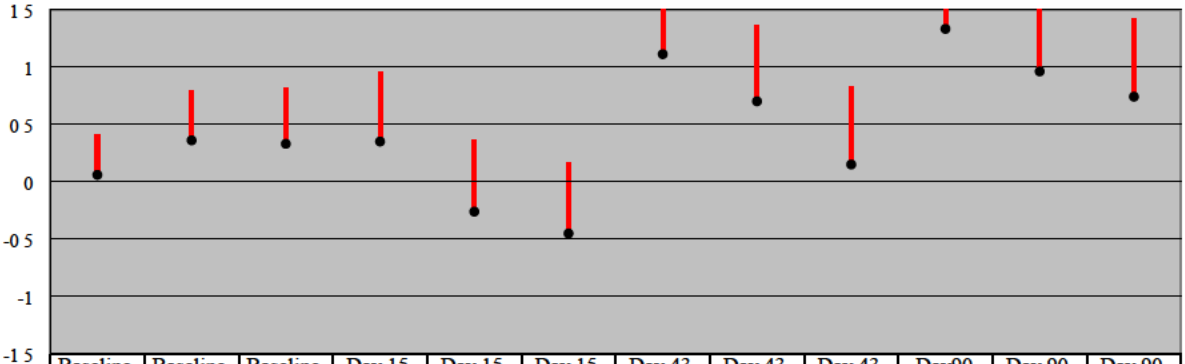
**Efficacy Results CS301– Primary Endpoint**

**Study AR-13324-CS301: Study Eye IOP (mmHg) By Visit (PP Population with Observed Data-Baseline IOP<27)**

| Day and Time | Mean IOP Netarsudil N=182 | Mean IOP Timolol N=188 | Mean Difference | 95% CI |
|---|---|---|---|---|
| | | | | |
| **Baseline** | | | | |
| 08:00 | 23.42<br>N=182 | 23.37<br>N=188 | 0.06 | (-0.29, 0.41) |
| 10:00 | 22.28<br>N=182 | 21.92<br>N=188 | 0.36 | (-0.07, 0.79) |
| 16:00 | 21.78<br>N=182 | 21.45<br>N=188 | 0.33 | (-0.15, 0.82) |
| | | | | |
| **Day 15** | | | | |
| 08:00 | 18.68<br>N=177 | 18.33<br>N=187 | 0.35 | (-0.27, 0.96) |
| 10:00 | 17.29 | 17.55 | -0.26 | (-0.87, 0.36) |

| Day and Time | Mean IOP Netarsudil N=182 | Mean IOP Timolol N=188 | Mean Difference | 95% CI |
|---|---|---|---|---|
| | N=176 | N=186 | | |
| 16:00 | 17.24 N=176 | 17.70 N=186 | -0.45 | (-1.08, 0.17) |
| | | | | |
| **Day 43** | | | | |
| 08:00 | 19.35 N=170 | 18.24 N=184 | 1.11 | (0.42, 1.80) |
| 10:00 | 18.14 N=170 | 17.44 N=184 | 0.70 | (0.04, 1.36) |
| 16:00 | 17.86 N=170 | 17.71 N=183 | 0.15 | (-0.52, 0.83) |
| | | | | |
| **Day 90** | | | | |
| 08:00 | 19.81 N=157 | 18.47 N=181 | 1.33 | (0.64, 2.03) |
| 10:00 | 18.92 N=158 | 17.96 N=181 | 0.96 | (0.26, 1.66) |
| 16:00 | 18.48 N=158 | 17.74 N=181 | 0.74 | (0.07, 1.42) |

**Study AR-13324-CS301: Mean IOP - PP Population (Baseline IOP<27)**



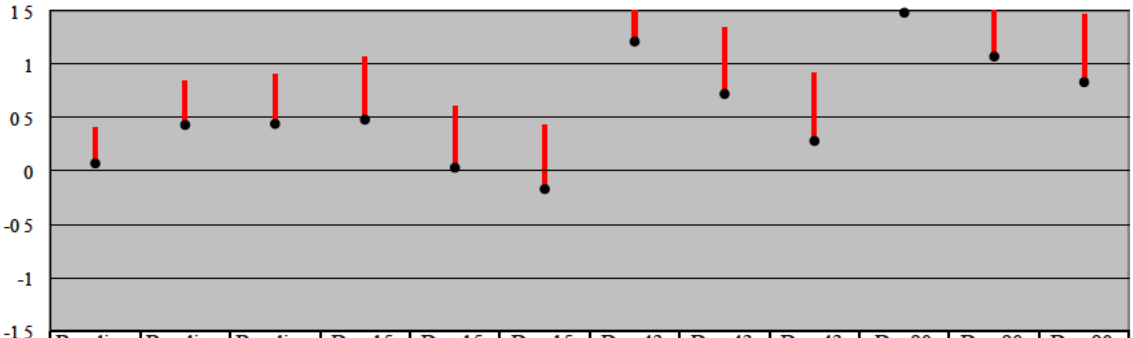

| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | -0.29 | -0.07 | -0.15 | -0.27 | -0.87 | -1.08 | 0.42 | 0.04 | -0.52 | 0.64 | 0.26 | 0.07 |
| Upper CI | 0.41 | 0.79 | 0.82 | 0.96 | 0.36 | 0.17 | 1.8 | 1.36 | 0.83 | 2.03 | 1.66 | 1.42 |
| Mean Difference | 0.06 | 0.36 | 0.33 | 0.35 | -0.26 | -0.45 | 1.11 | 0.7 | 0.15 | 1.33 | 0.96 | 0.74 |

Non-inferiority of netarsudil ophthalmic solution 0.02% dosed QD to timolol maleate ophthalmic solution 0.5% dosed BID was not demonstrated in the PP population (baseline IOP < 27 mmHg). The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points, therefore it did not meet the pre-specified criteria for non-inferiority.

**Study AR-13324-CS301: Study Eye IOP (mmHg) by Visit (ITT with LOCF Population)**

| Day and Time | Mean IOP Netarsudil QD N=202 | Mean IOP Timolol BID N=209 | Mean Difference Between Netarsudil and Timolol | 95% CI |
|---|---|---|---|---|
| **Baseline (Visit 3)** | | | | |
| 08:00 | 23.41 | 23.34 | 0.07 | (-0.27, 0.41) |
| 10:00 | 22.30 | 21.87 | 0.43 | (0.02, 0.84) |
| 16:00 | 21.84 | 21.40 | 0.44 | (-0.02, 0.90) |
| | | | | |
| **Day 15** | | | | |
| 08:00 | 18.81 | 18.33 | 0.48 | (-0.11, 1.07) |
| 10:00 | 17.54 | 17.51 | 0.03 | (-0.56, 0.61) |
| 16:00 | 17.50 | 17.68 | -0.17 | (-0.77, 0.43) |
| | | | | |
| **Day 43** | | | | |
| 08:00 | 19.46 | 18.26 | 1.21 | (0.56, 1.86) |
| 10:00 | 18.22 | 17.50 | 0.72 | (0.10, 1.34) |
| 16:00 | 18.07 | 17.79 | 0.28 | (-0.36, 0.91) |
| | | | | |
| **Day 90** | | | | |
| 08:00 | 19.97 | 18.48 | 1.48 | (0.85, 2.12) |
| 10:00 | 19.03 | 17.96 | 1.07 | (0.43, 1.71) |
| 16:00 | 18.68 | 17.85 | 0.83 | (0.20, 1.46) |

**Study AR-13324-CS301: Mean IOP - ITT with LOCF Population (Baseline IOP<27)**




| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | -0.27 | 0.02 | -0.02 | -0.11 | -0.56 | -0.77 | 0.56 | 0.1 | -0.36 | 0.85 | 0.43 | 0.2 |
| Upper CI | 0.41 | 0.84 | 0.9 | 1.07 | 0.61 | 0.43 | 1.86 | 1.34 | 0.91 | 2.12 | 1.71 | 1.46 |
| Mean Difference | 0.07 | 0.43 | 0.44 | 0.48 | 0.03 | -0.17 | 1.21 | 0.72 | 0.28 | 1.48 | 1.07 | 0.83 |

The ITT population (N = 411 subjects) was similar in size to the PP population (N = 370 subjects), and the degree of change from diurnally adjust baseline values at each of the 9 observation time points at Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) was also similar. It was also true, as for the PP population, that netarsudil did not demonstrate non-inferiority to timolol in the ITT population. This submission is of sufficient quality to allow for a substantive review.

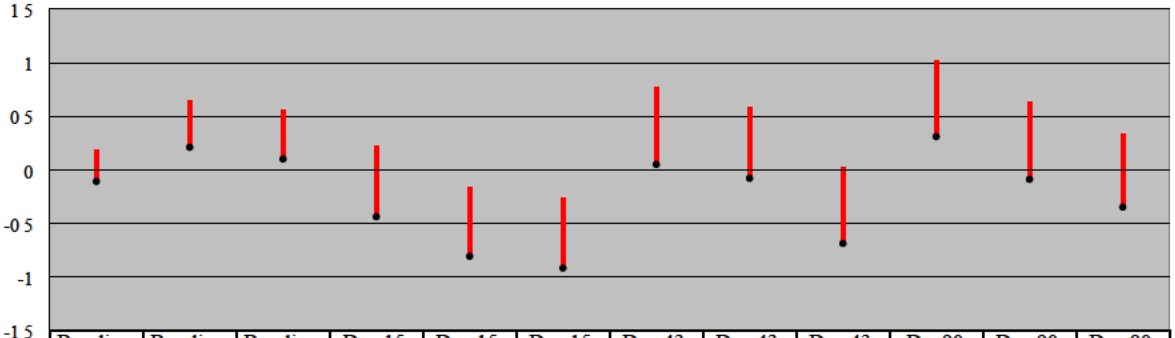
## Additional Analysis Conducted on Study AR-13324-CS301

For Study AR-13324-CS301 there was a post hoc efficacy analysis of subgroups with maximum baseline IOP < 25 mmHg.

**Study AR-13324-CS301: Study Eye Mean IOP (mmHg) By Visit for Subjects with Baseline IOP <25 at All Timepoints, POST HOC ANALYSIS (PP Population with Observed Data)**

| Day and Time | Mean IOP Netarsudil QD N=113 | Mean IOP Timolol BID N=124 | Mean Difference | 95% CI |
|---|---|---|---|---|
| **Baseline (Visit 3)** | | | | |
| 08:00 | 22.39 | 22.50 | -0.11 | (-0.39, 0.18) |
| 10:00 | 21.28 | 21.07 | 0.21 | (-0.21, 0.64) |
| 16:00 | 20.62 | 20.52 | 0.10 | (-0.36, 0.56) |
| | | | | |
| **Day 15** | | | | |
| 08:00 | 17.34 | 17.78 | -0.44 | (-1.10, 0.22) |
| 10:00 | 16.18 | 16.98 | -0.81 | (-1.44, -0.17) |
| 16:00 | 16.22 | 17.14 | -0.92 | (-1.58, -0.26) |
| | | | | |
| **Day 43** | | | | |
| 08:00 | 17.85 | 17.81 | 0.05 | (-0.68, 0.77) |
| 10:00 | 16.88 | 16.96 | -0.08 | (-0.74, 0.58) |
| 16:00 | 16.57 | 17.26 | -0.69 | (-1.40,0.02) |
| | | | | |
| **Day 90** | | | | |
| 08:00 | 18.22 | 17.91 | 0.31 | (-0.40, 1.02) |
| 10:00 | 17.34 | 17.43 | -0.09 | (-0.82, 0.63) |
| 16:00 | 17.02 | 17.37 | -0.35 | (-1.03, 0.34) |

**Study AR-13324-CS301: Mean IOP by Visit for Subjects with Baseline IOP <25 - PP Population**




| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | -0.39 | -0.21 | -0.36 | -1.1 | -1.44 | -1.58 | -0.68 | -0.74 | -1.4 | -0.4 | -0.82 | -1.03 |
| Upper CI | 0.18 | 0.64 | 0.56 | 0.22 | -0.17 | -0.26 | 0.77 | 0.58 | 0.02 | 1.02 | 0.63 | 0.34 |
| Mean Difference | -0.11 | 0.21 | 0.1 | -0.44 | -0.81 | -0.92 | 0.05 | -0.08 | -0.69 | 0.31 | -0.09 | -0.35 |

Netarsudil ophthalmic solution, 0.02% dosed qd was non-inferior to timolol maleate ophthalmic solution, 0.5% dosed bid in a post hoc analysis of subjects with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for differences in mean IOP was within 1.5 mmHg at all 9 time points and within 1.0 mmHg at 8 of the 9 time points.

**Study AR-13324-CS302: A double-masked, randomized, multi-center, active-controlled, parallel, 12-month study assessing the safety and ocular hypotensive efficacy of AR-13324 Ophthalmic Solution, 0.02% QD and BID compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure**

The primary efficacy outcome was the mean IOP for subjects with baseline IOP > 20 mmHg (08:00 hours) and < 25 mmHg (at 08:00, 10:00, and 16:00 hours) in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits.

See Section 10 of this review regarding Pediatrics. Only two pediatric subjects, 11 and 14 years of age, were enrolled in one Phase 3 trial, StudyAR-13324-CS302.

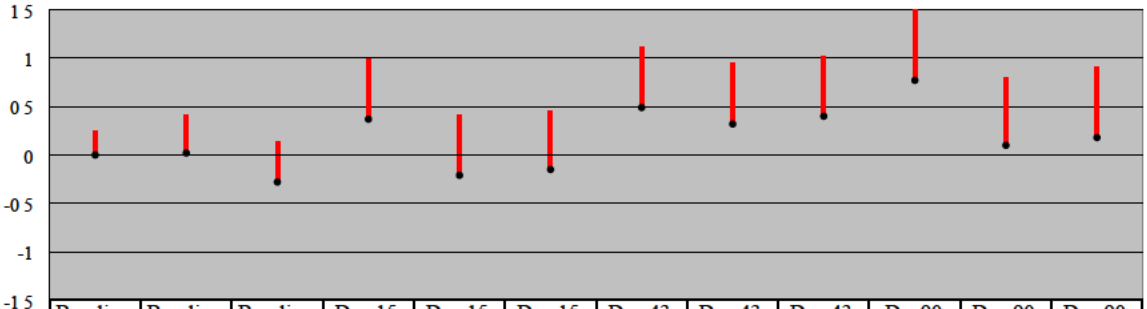
**Efficacy Results CS302– Primary Endpoint**

**Study AR-13324-CS302: Study Eye IOP (mmHg) By Visit (PP Population With Observed Data With Baseline IOP <25 MmHg)**

| Day and Time | Mean IOP Netarsudil 0.02% QD | Mean IOP Netarsudil 0.02% BID | Mean IOP Timolol 0.5% BID | Mean Difference From Timolol Netarsudil 0.02% QD | 95% CI | Mean Difference From Timolol Netarsudil 0.02% BID | 95% CI |
|---|---|---|---|---|---|---|---|
| **Baseline (Visit 3)** | | | | | | | |
| 08:00 | 22.54 N=129 | 22.55 N=132 | 22.54 N=142 | 0 | (-0.25, 0.25) | 0.01 | (-0.24, 0.26) |
| 10:00 | 21.29 N=129 | 21.27 N=132 | 21.27 N=142 | 0.02 | (-0.37, 0.41) | -0.01 | (-0.40, 0.38) |
| 16:00 | 20.43 N=129 | 20.56 N=132 | 20.71 N=142 | -0.28 | (-0.71, 0.14) | -0.15 | (-0.58, 0.29) |
| | | | | | | | |
| **Day 15** | | | | | | | |
| 08:00 | 18.07 N=127 | 17.21 N=122 | 17.69 N=142 | 0.37 | (-0.25, .99) | -0.48 | (-1.19, 0.22) |
| 10:00 | 16.72 N=126 | 16.35 N=120 | 16.93 N=141 | -0.21 | (-0.82, 0.41) | -0.57 | (-1.24, 0.09) |
| 16:00 | 16.68 N=126 | 15.65 N=118 | 16.83 N=141 | -0.15 | (-0.75, 0.46) | -1.18 | (-1.82, -0.54) |

| Day and Time | Mean IOP Netarsudil 0.02% QD | Mean IOP Netarsudil 0.02% BID | Mean IOP Timolol 0.5% BID | Mean Difference From Timolol Netarsudil 0.02% QD | 95% CI | Mean Difference From Timolol Netarsudil 0.02% BID | 95% CI |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| **Day 43** | | | | | | | |
| 08:00 | 17.95 N=122 | 17.64 N=111 | 17.46 N=141 | 0.49 | (-0.13, 1.12) | 0.17 | (-0.51, 0.86) |
| 10:00 | 16.95 N=120 | 16.28 N=106 | 16.63 N=141 | 0.32 | (-0.31, 0.95) | -0.34 | (-1.02, 0.33) |
| 16:00 | 17.00 N=120 | 15.75 N=106 | 16.60 N=141 | 0.40 | (-0.22, 1.02) | -0.85 | (-1.53, -0.17) |
| | | | | | | | |
| **Day 90** | | | | | | | |
| 08:00 | 18.24 N=116 | 17.58 N=91 | 17.47 N=140 | 0.77 | (0.03, 1.50) | 0.11 | (-0.64, 0.86) |
| 10:00 | 17.03 N=114 | 16.94 N=88 | 16.92 N=140 | 0.10 | (-0.59, 0.80) | 0.02 | (-0.72, 0.77) |
| 16:00 | 17.13 N=114 | 16.51 N=88 | 16.95 N=139 | 0.18 | (-0.55, 0.91) | -0.44 | (-1.16, 0.27) |

**Study AR-13324-CS302: Mean IOP (Netarsudil 0.02% QD Compared to Timolol 0.5% BID) from Baseline - PP Population (Baseline IOP<25**



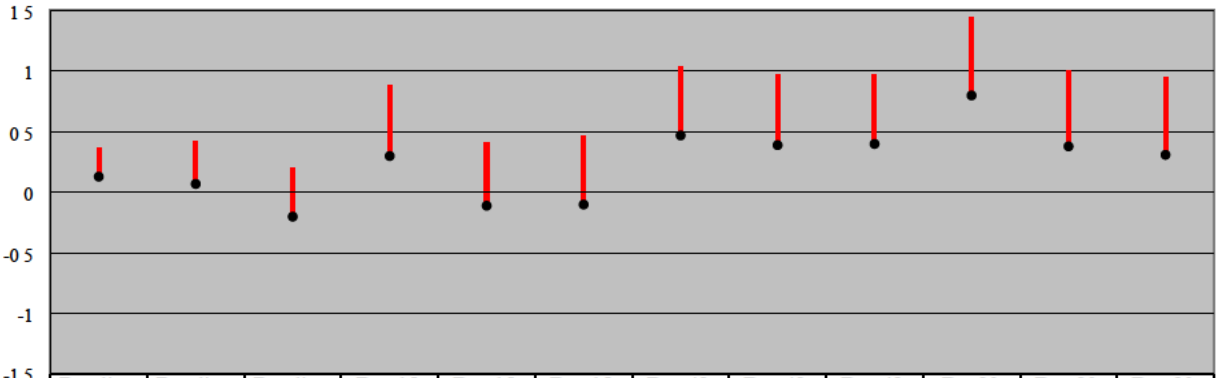

| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | -0.25 | -0.37 | -0.71 | -0.25 | -0.82 | -0.75 | -0.13 | -0.31 | -0.22 | 0.03 | -0.59 | -0.55 |
| Upper CI | 0.25 | 0.41 | 0.14 | 0.99 | 0.41 | 0.46 | 1.12 | 0.95 | 1.02 | 1.5 | 0.8 | 0.91 |
| Mean Difference | 0 | 0.02 | -0.28 | 0.37 | -0.21 | -0.15 | 0.49 | 0.32 | 0.4 | 0.77 | 0.1 | 0.18 |

Non-inferiority of netarsudil QD and BID to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority. The upper 95% confidence limit for the differences in mean IOP between netarsudil BID and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at all of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority.

**Study AR-13324-CS302: Study Eye IOP (mmHg) By Visit (ITT with LOCF With Baseline IOP <25 MmHg)**

| Day and Time | Mean IOP Netarsudil 0.02% QD | Mean IOP Netarsudil 0.02% BID | Mean IOP Timolol 0.5% BID | Mean Difference From Timolol Netarsudil 0.02% QD | 95% CI | Mean Difference From Timolol Netarsudil 0.02% BID | 95% CI |
|---|---|---|---|---|---|---|---|
| **Baseline** | | | | | | | |
| 08:00 | 22.54 | 22.56 | 22.41 | 0.13 | (-0.10, 0.37) | 0.15 | (-0.10, 0.39) |
| 10:00 | 21.23 | 21.28 | 21.16 | 0.07 | (-0.28, 0.42) | 0.11 | (-0.24, 0.47) |
| 16:00 | 20.40 | 20.59 | 20.60 | -0.20 | (-0.60, 0.20) | -0.01 | (-0.41, 0.40) |
| | | | | | | | |
| **Day 15** | | | | | | | |
| 08:00 | 17.91 | 17.69 | 17.61 | 0.30 | (-0.28, 0.88) | 0.07 | (-0.58, 0.73) |
| 10:00 | 16.75 | 16.81 | 16.92 | -0.17 | (-0.74, 0.41) | -0.11 | (-0.74, 0.52) |
| 16:00 | 16.73 | 16.34 | 16.83 | -0.10 | (-0.67, 0.47) | -0.49 | (-1.12, 0.14) |
| | | | | | | | |
| **Day 43** | | | | | | | |
| 08:00 | 17.85 | 17.97 | 17.38 | 0.47 | (-0.09, 1.04) | 0.60 | (-0.03, 1.22) |
| 10:00 | 16.93 | 17.06 | 16.54 | 0.39 | (-0.18, 0.97) | 0.52 | (-0.10, 1.14) |
| 16:00 | 16.96 | 16.38 | 16.56 | 0.40 | (-0.16, 0.97) | -0.18 | (-0.82, 0.46) |
| | | | | | | | |
| **Day 90** | | | | | | | |
| 08:00 | 18.16 | 18.13 | 17.36 | 0.80 | (0.15, 1.45) | 0.77 | (-0.09, 1.44) |
| 10:00 | 17.15 | 17.35 | 16.77 | 0.38 | (-0.25, 1.01) | 0.58 | (-0.06, 1.21) |
| 16:00 | 17.11 | 16.80 | 16.79 | 0.31 | (-0.32, 0.95) | 0.00 | (-0.63, 0.64) |

**Study AR-13324-CS302: Mean IOP (Netarsudil 0.02% QD Comparred to Timolol 0.5% BID) - ITT with LOCF Population (Baseline IOP<25)**




| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | -0.1 | -0.28 | -0.6 | -0.28 | -0.74 | -0.67 | -0.09 | -0.18 | -0.16 | 0.15 | -0.25 | -0.32 |
| Upper CI | 0.37 | 0.42 | 0.2 | 0.88 | 0.41 | 0.47 | 1.04 | 0.97 | 0.97 | 1.45 | 1.01 | 0.95 |
| Mean Difference | 0.13 | 0.07 | -0.2 | 0.3 | -0.11 | -0.1 | 0.47 | 0.39 | 0.4 | 0.8 | 0.38 | 0.31 |

As for the PP population, both netarsudil QD and BID demonstrated non-inferiority to timolol in the ITT population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 7 of the 9 time points and the upper 95% confidence limit for the differences in mean IOP between netarsudil BID and timolol was within 1.0 mmHg at all of the 9 time points. This submission is of sufficient quality to allow for a substantive review.

**Study AR-13324-CS304: A double-masked, randomized, multi-center, active-controlled, parallel group, 6-month study with a 3-month interim analysis assessing the ocular hypotensive efficacy and safety of AR-13324 Ophthalmic Solution, 0.02% QD compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure**

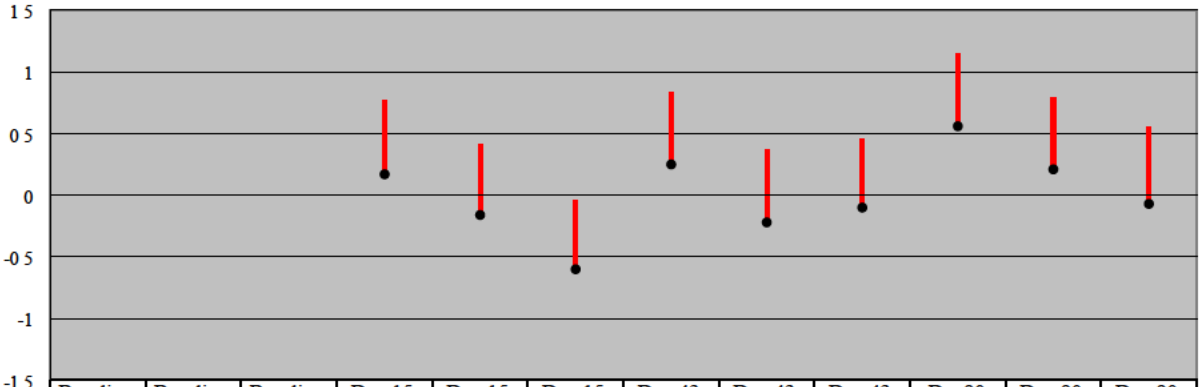
The primary efficacy endpoint was the mean IOP at the following time points: 08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits (the primary efficacy population, as defined in the SAP, was the PP population with maximum baseline IOP of <25 mmHg).

**Efficacy Results CS304– Primary Endpoint**

**Study AR-13324-CS304: Study Eye Mean IOP (mmHg) By Visit (PP Population With Observed Data-Baseline IOP<25)**

| Day and Time | Mean IOP Netarsudil 0.02% QD | Mean IOP Timolol 0.5% BID | Mean Difference | 95% CI |
|---|---|---|---|---|
| **Baseline** | | | | |
| 08:00 | 22.40 N=186 | 22.44 N=186 | | |
| 10:00 | 21.06 N=186 | 21.27 N=186 | | |
| 16:00 | 20.69 N=186 | 20.69 N=186 | | |
| **Day 15** | | | | |
| 08:00 | 17.68 N=184 | 17.51 N=183 | 0.17 | (-0.43, 0.77) |
| 10:00 | 16.55 N=181 | 16.71 N=183 | -0.16 | (-0.73, 0.41) |
| 16:00 | 16.32 N=181 | 16.92 N=183 | -0.60 | (-1.16, -0.04) |
| **Day 43** | | | | |
| 08:00 | 17.84 N=177 | 17.60 N=183 | 0.25 | (-0.34, 0.83) |
| 10:00 | 16.75 N=177 | 16.98 N=182 | -0.22 | (-0.82, 0.37) |
| 16:00 | 16.57 N=176 | 16.67 N=182 | -0.10 | (-0.66, 0.46) |
| **Day 90** | | | | |
| 08:00 | 17.86 N=167 | 17.29 N=179 | 0.56 | (-0.02, 1.15) |
| 10:00 | 16.90 N=167 | 16.69 N=179 | 0.21 | (-0.37, 0.79) |
| 16:00 | 16.73 N=165 | 16.80 N=179 | -0.07 | (-0.68, 0.55) |

**Study AR-13324-CS304: Mean IOP - PP Population (Baseline IOP<25)**



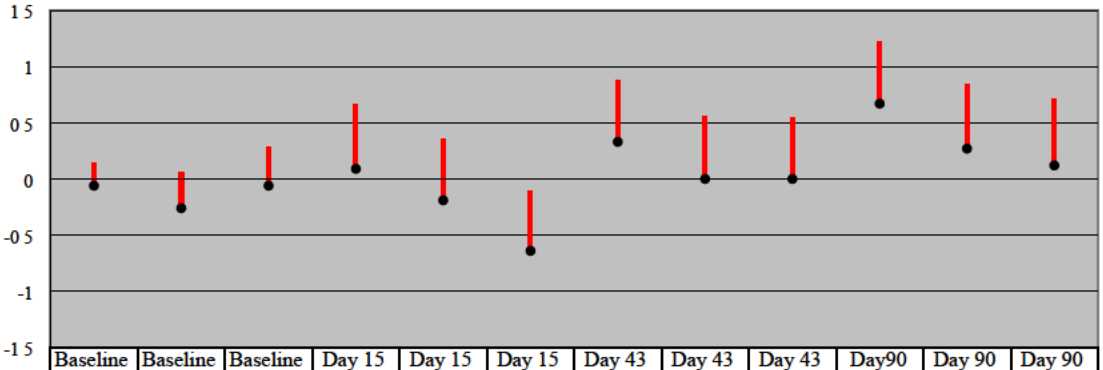

| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | | | | -0.43 | -0.73 | -1.16 | -0.34 | -0.82 | -0.66 | -0.02 | -0.37 | -0.68 |
| Upper CI | | | | 0.77 | 0.41 | -0.04 | 0.83 | 0.37 | 0.46 | 1.15 | 0.79 | 0.55 |
| Mean Difference | | | | 0.17 | -0.16 | -0.6 | 0.25 | -0.22 | -0.1 | 0.56 | 0.21 | -0.07 |

Netarsudil demonstrated non-inferiority to timolol in both the PP population with maximum baseline IOP < 25 mmHg.

**Study AR-13324-CS304: Study Eye Mean IOP (mmHg) by Visit (ITT with LOCF Population)**

| Day and Time | Mean IOP Netarsudil 0.02% QD N=214 | Mean IOP Timolol 0.5% BID N=209 | Mean Difference Between netarsudil and Timolol | 95% CI |
|---|---|---|---|---|
| **Baseline (Visit 3)** | | | | |
| 08:00 | 22.37 | 22.44 | -0.06 | (-0.27, 0.14) |
| **10:00** | 21.02 | 21.28 | -0.26 | (-0.59, 0.06) |
| **16:00** | 20.61 | 20.67 | -0.06 | (-0.42, 0.29) |
| | | | | |
| **Day 15** | | | | |
| **08:00** | 17.58 | 17.49 | 0.09 | (-0.47, 0.66) |
| **10:00** | 16.49 | 16.68 | -0.19 | (-0.74, 0.36) |
| **16:00** | 16.22 | 16.86 | -0.64 | (-1.17, -0.11) |
| | | | | |
| **Day 43** | | | | |
| **08:00** | 17.82 | 17.49 | 0.33 | (-0.21, 0.88) |
| **10:00** | 16.84 | 16.84 | 0 | (-0.57, 0.56) |
| **16:00** | 16.62 | 16.62 | 0 | (-0.55, 0.55) |
| | | | | |
| **Day 90** | | | | |
| **08:00** | 17.94 | 17.28 | 0.67 | (0.11, 1.22) |
| **10:00** | 16.93 | 16.66 | 0.27 | (-0.29, 0.84) |
| **16:00** | 16.86 | 16.73 | 0.12 | (-0.46, 0.71) |

**Study AR-13324-CS304: Mean IOP - ITT with LOCF Population (Baseline IOP<25)**




| | Baseline (08:00) | Baseline (10:00) | Baseline (16:00) | Day 15 (08:00) | Day 15 (10:00) | Day 15 (16:00) | Day 43 (08:00) | Day 43 (10:00) | Day 43 (16:00) | Day90 (08:00) | Day 90 (10:00) | Day 90 (16:00) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lower CI | -0.27 | -0.59 | -0.42 | -0.47 | -0.74 | -1.17 | -0.21 | -0.57 | -0.55 | 0.11 | -0.29 | -0.46 |
| Upper CI | 0.14 | 0.06 | 0.29 | 0.66 | 0.36 | -0.11 | 0.88 | 0.56 | 0.55 | 1.22 | 0.84 | 0.71 |
| Mean Difference | -0.06 | -0.26 | -0.06 | 0.09 | -0.19 | -0.64 | 0.33 | 0 | 0 | 0.67 | 0.27 | 0.12 |

Netarsudil demonstrated non-inferiority to timolol in the ITT population as well with maximum baseline IOP < 25 mmHg. This submission is of sufficient quality to allow for a substantive review.

**Biostatistics Review of Secondary Endpoints**

The Biostatistical Reviewer agreed that all three studies demonstrated that Rhopressa QD was efficacious in reducing elevated intraocular pressure; but Rhopressa QD was less efficacious compared to timolol 0.5% BID for subjects with higher maximum baseline IOP (≥ 25 mmHg). The Reviewer conducted analyses of the secondary endpoint of mean IOP changes from baseline based on ANCOVA adjusted analyses for each trial evaluating subjects with baseline IOP <25 mmHg and subjects with baseline IOP ≥ 25 mmHg separately.

Study AR-13324-CS301: For subjects with baseline IOP <25 mmHg, the two treatment groups had similar mean IOP reductions; mean IOP reduction from baseline ranged from 3.6 to 5.1 mmHg in the Rhopressa group; and from 3.2 to 4.7 mmHg in the timolol group. For subjects with baseline IOP ≥ 25 mmHg, mean IOP reduction from baseline ranged from 2.2 to 4.9 mmHg in the Rhopressa group; and from 4.6 to 6.0 mmHg in the timolol group. Compared with timolol, the Rhopressa group had a smaller mean IOP reduction at all morning time points, and on Days 43 and 90.

Study AR-13324-CS302: For subjects with baseline IOP <25 mmHg, The two treatment groups had similar mean IOP reductions; mean IOP reduction from baseline ranged from 3.4 to 4.6 mmHg in the netarsudil group; and from 3.7 to 5.1 mmHg in the timolol group. For subjects with baseline IOP ≥ 25 mmHg, mean IOP reduction from baseline ranged from 3.4 to 4.9 mmHg in the netarsudil group; and from 4.3 to 5.6 mmHg in the timolol group. Compared with timolol, the netarsudil group had a smaller mean IOP reduction at all morning time points, and on Days 43 and 90.

Study AR-13324-CS304: For subjects with baseline IOP <25 mmHg, The two treatment groups had similar mean IOP reductions; mean IOP reduction from baseline ranged from 3.9 to 4.7 mmHg in the netarsudil group; and from 3.8 to 5.2 mmHg in the timolol group. For subjects with baseline IOP ≥ 25 mmHg, mean IOP reduction from baseline ranged from 3.9 to 5.0 mmHg in the Rhopressa group; and from 4.9 to 6.2 mmHg in the timolol group. Compared with timolol, the Rhopressa group had a smaller mean IOP reduction at all time points, particularly the morning time points on Days 43 and 90.

**Efficacy Summary Statement**
Study 301 failed in its primary endpoint and netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. It did, however, demonstrate that netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post hoc analysis. Netarsudil did have an IOP lowering effect at baseline IOPs ≥ 25, but was not statistically non-inferior to timolol when including these patients.

Study 302 achieved success in its primary endpoint and demonstrated that netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg. Netarsudil did have an IOP lowering effect at baseline IOPs ≥ 25, but was not statistically non-inferior to timolol when including these patients.

Study 304 achieved success in its primary endpoint and demonstrated that netarsudil was non-inferior to timolol in patients with a baseline IOP < 30 mmHg in the PP population, but this result was not replicated in the ITT population. In a secondary endpoint analysis, noninferiority of netarsudil to timolol was demonstrated in baseline IOP < 25 mmHg in both PP and ITT populations.

These conclusions regarding the analyses of the primary endpoint are supported by sensitivity analyses conducted by the Biostatistical Reviewer. In addition, analyses of the secondary enpoint of mean IOP change from baseline evaluating subjects with baseline IOP <25 mmHg and subjects with baseline IOP ≥ 25 mmHg separately support these conclusions.

The data contained in this submission establishes the efficacy of netarsudil ophthalmic solution, 0.02% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

# 8. Safety

Although all submitted studies were reviewed, the primary support for safety is from three clinical studies (Studies AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304). See the Medical Officer's review in DARRTS dated 11/8/2017.

**OVERALL EXPOSURE**

**Study AR-13324-CS301: Exposure to Study Medication by Treatment Group (Safety Population)**

| | **Netarsudil 0.02% QD N=203** | **Timolol 0.5% BID N=208** |
|---|---|---|
| **Days of Exposure** | | |
| Mean (sd) | 82.8 | 87.4 |
| Minimum | 3 | 4 |
| Maximum | 112 | 138 |

**Study AR-13324-CS302: Exposure to Study Medication by Treatment Group (Safety Population)**

| | **Netarsudil 0.02% QD N=251** | **Netarsudil 0.02% BID N=253** | **Timolol 0.5% BID N=251** |
|---|---|---|---|
| **Days of Exposure** | | | |
| Mean (sd) | 259.7 | 185.2 | 324.5 |
| Minimum | 1 | 2 | 1 |
| Maximum | 385 | 375 | 371 |

**Study AR-13324-CS304: Exposure to Study Medication by Treatment Group (Safety Population)**

| | **Netarsudil 0.02% QD N=351** | **Timolol 0.5% BID N=357** |
|---|---|---|
| **Days of Exposure** | | |
| Mean (sd) | 147.4 | 167.7 |
| Minimum | 1 | 2 |
| Maximum | 1197 | 197 |

**DEATHS**

Study AR-13324-CS301: No deaths occurred during the study.

Study AR-13324-CS302: Two subjects in the netarsudil QD treatment group died during the course of the study secondary to a myocardial infarction.

Study AR-13324-CS304: One subject in the netarsudil QD group died during the study secondary to cardiac arrest.

None of these deaths appear attributable to the use of the study drug.

**DROPOUTS AND/OR DISCONTINUATIONS DUE TO ADVERSE EFFECTS**

## Study AR-13324-CS301: Subject Disposition (ITT Population)

| **Number of Randomized Subjects** | **Netarsudil 0.02% N=202** | **Timolol 0.5% N=209** |
|---|---|---|
| Study Completion | | |
| Completed | 171 (85%) | 196 (94%) |
| Discontinued | 31 (15%) | 13 (6%) |
| | | |
| Reason for Subject Discontinuation | | |
| Adverse Event | 20 (65%) | 4 (31%) |
| Withdrawal of Consent | 3 (10%) | 2 (15%) |
| Non-compliant | 0 | 1 (8%) |
| Lost to Follow-up | 0 | 1 (8%) |
| Lack of Efficacy | 3 (10%) | 0 |
| Investigator Decision | 2 (7%) | 0 |
| Protocol Violation | 3 (10%) | 5 (39%) |

## Study AR-13324-CS302: Subject Disposition (ITT Population)

| **Number of Randomized Subjects** | **Netarsudil 0.02% QD N=251** | **Netarsudil 0.02% BID N=254** | **Timolol 0.5% BID N=251** |
|---|---|---|---|
| Study Completion | | | |
| Completed Month 3 | 205 (82%) | 153 (61%) | 237 (94%) |
| Discontinued Prior to Month 3 | 46 (18%) | 101 (40%) | 14 (6%) |
| | | | |
| Completed Month 12 | 146 (58%) | 86 (34%) | 204 (81%) |
| Discontinued Prior to Month 12 | 105 (42%) | 168 (66%) | 47 (19%) |
| | | | |
| Reason for Subject Discontinuation | | | |
| Adverse Event | 71 (67%) | 132 (79%) | 15 (32%) |
| Withdrawal of Consent | 9 (9%) | 13 (8%) | 9 (19%) |
| Non-compliant | 3 (3%) | 1 (1%) | 3 (6%) |
| Lost to Follow-up | 1 (1%) | 3 (2%) | 0 |
| Lack of Efficacy | 10 (10%) | 4 (2%) | 2 (4%) |
| Disallowed Concurrent Medication | 2 (2%) | 2 (1%) | 5 (11%) |
| Investigator Decision | 1 (1%) | 2 (1%) | 2 (4%) |
| Protocol Violation | 4 (4%) | 6 (4%) | 10 (21%) |
| Death | 2 (2%) | 0 | 0 |
| Other | 2 (2%) | 5 (3%) | 1 (2%) |

**Study AR-13324-CS304: Subject Disposition (ITT Population)**

| **Number of Randomized Subjects** | **Netarsudil 0.02% N=351** | **Timolol 0.5% N=357** |
|---|---|---|
| Study Completion | | |
| Completed | 243 (69%) | 314 (88%) |
| Discontinued | 108 (31%) | 43 (12%) |
| | | |
| Reason for Subject Discontinuation | | |
| Adverse Event | 68 (19%) | 4 (31%) |
| Withdrawal of Consent | 12 (3%) | 2 (15%) |
| Non-compliant | 1 | 1 (8%) |
| Lost to Follow-up | 1 | 1 (8%) |
| Lack of Efficacy | 12 (3%) | 0 |
| Disallowed concurrent Medication | 1 (0.3%) | 3 (1%) |
| Investigator Decision | 2 (1%) | 4(1%) |
| Protocol Violation | 5 (1%) | 4 (1%) |
| Death | 1 (0.3%) | 0 |
| Other | 5 (1%) | 2 (1%) |

**NONFATAL SERIOUS ADVERSE EVENTS**

**Study AR-13324-CS301: Serious Treatment Emergent AEs**

| **Subject Number/Treatment Group** | **Outcome** | **SAE** |
|---|---|---|
| 108-016 Timolol | Recovered/Resolved | Worsening of adenomyosis |
| 112-010 Timolol | Both events resolved/resolved | CHF<br>Left upper extremity numbness |
| 116-009 Timolol | Not recovered/resolved | CVA |
| 123-011 Rhopressa | Not recovered/resolved | Prostate CA |
| 128-002 Rhopressa | Recovered/Resolved | Exacerbation of CAD |
| 128-003 Rhopressa | Recovered/Resolved | HTN |
| 135-001 Rhopressa | Both events recovered/Resolved | Pneumonia<br>Acute respiratory failure |

Nine serious TEAEs were reported among 3 subjects in the netarsudil group and 4 subjects in the timolol group. The only serious TEAE considered by the Investigator to be possibly related to study medication was exacerbation of coronary artery disease in a subject instilling netarsudil ophthalmic solution, 0.02% that reported chest pain as a TEAE.

## Study AR-13324-CS302: Serious Treatment Emergent AEs

| Subject Number/Treatment Group | Outcome | SAE |
|---|---|---|
| 202-003<br>Timolol | Both events recovered/resolved with sequelae | Peripheral artery occlusion<br>Fall |
| 204-041<br>Timolol | Recovered/Resolved | Renal failure |
| 206-022<br>Rhopressa QD | Both events recovered/ resolved with sequelae | Cholelithiasis<br>Exacerbation of CAD |
| 209-002<br>Rhopressa QD | Recovered/Resolved | Myelodysplastic syndrome |
| 209-002<br>Rhopressa BID | Recovered/Resolved | MI |
| 211-004<br>Rhopressa QD | Recovered/Resolved with sequelae | Breast CA |
| 212-006<br>Rhopressa BID | Both events recovered/resolved | Pneumonia<br>Pulmonary embolism |
| 212-016<br>Rhopressa QD | Recovered/Resolved | Broken foot<br>Acute renal failure |
| 213-003<br>Timolol | Recovered/Resolved | Worsening of CAD |
| 216-001<br>Rhopressa BID | Recovered/Resolved | Worsening of cataract |
| 217-021<br>Timolol | Fatal | MI |
| 217-026<br>Rhopressa QD | Recovered/Resolved with sequelae | CAD |
| 218-021<br>Rhopressa BID | Recovered/Resolved | Perforated gastric ulcer |
| 222-010<br>Timolol | Recovered/Resolved | Worsening of arthritis |
| 226-012<br>Rhopressa BID | Recovered/Resolved | MI |
| 227-015<br>Timolol | Recovered/Resolved | CVA<br>Atrial fibrillation |
| 228-005<br>Timolol | Recovered/Resolved with sequelae | Back pain |
| 228-006<br>Rhopressa BID | Recovered/Resolved | Bacterial peritonitis<br>UTI |
| 230-014<br>Rhopressa QD | Recovered/Resolved | Angioedema |
| 231-006<br>Rhopressa<br>BID | Recovered/Resolved | Carotid artery stenosis |
| 234-019<br>Rhopressa QD | Recovered/Resolved | Internal bleeding secondary to motor vehicle accident |
| 238-001<br>Timolol | Recovered/Resolved | Melanoma |
| 239-003<br>Timolol | All events recovered/resolved | Pulmonary artery stenosis<br>Atrial flutter<br>Bradycardia<br>Fluid overload |
| 244-001 | Recovered/Resolved | Ligament rupture |

| **Subject Number/Treatment Group** | **Outcome** | **SAE** |
|---|---|---|
| Rhopressa BID | | |
| 246-005<br>Timolol | Recovered/Resolved with sequelae | Embolic stroke |
| 248-030<br>Timolol | Recovered/Resolved | Prostate CA |
| 250-005<br>Rhopressa QD | Recovered/Resolved | Abdominal pain |
| 251-010<br>Rhopressa QD | Recovered/Resolved | Epistaxis |
| 251-044<br>Timolol | Recovered/Resolved | Cellulitis |
| 254-008<br>Timolol | Recovered/Resolved | Post-operative ileus |
| 258-002<br>Timolol | Fatal | MI |
| 262-016<br>Rhopressa BID | Recovered/Resolved | Cholecystitis |
| 262-020<br>Timolol | Recovered/Resolved | HTN |
| 262-027<br>Rhopressa BID | Recovered/Resolved | Hip fracture |
| 262-045<br>Rhopressa BID | Both events recovered/resolved | Worsening of PSA<br>Synovial cyst |
| 263-011<br>Timolol | Recovered/Resolved | Atrial fibrillation |

A total of 49 serious TEAEs were reported in this 12-month study: 22 events in 17 (6.8%) of netarsudil QD subjects, 9 events in 7 (2.8%) netarsudil BID subjects, and 18 events in 12 (4.8%) timolol subjects (Table 14.3.3.2). Only one serious TEAE occurred in the Eye Disorders system organ class; cataract requiring surgery was reported in a subject treated with timolol.

## Study AR-13324-CS304: Serious Treatment Emergent AEs (6 month report)

Table 14.3.3.2
Number and Percentage of Subjects with Serious Adverse Events, by Treatment Group, System Organ Class, and Preferred Term
Safety Population -- All Subjects

| System Organ Class (SOC)<br>Preferred Term (PT) | Netarsudil 0.02% QD (N=351)<br>n (%) | Timolol 0.5% BID (N=357)<br>n (%) | All Subjects (N=708)<br>n (%) | p-value[1] |
|---|---|---|---|---|
| Any Serious TEAEs | 8 ( 2.3) | 10 ( 2.8) | 18 ( 2.5) | 0.8123 |
| Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) | 3 ( 0.9) | 2 ( 0.6) | 5 ( 0.7) | 0.6840 |
| Bladder Cancer Recurrent | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Chronic Myeloid Leukaemia | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Invasive Ductal Breast Carcinoma | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Papillary Thyroid Cancer | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Uterine Leiomyoma | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Cardiac Disorders | 2 ( 0.6) | 2 ( 0.6) | 4 ( 0.6) | >0.9999 |
| Atrial Fibrillation | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Cardiac Arrest | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Cardiomegaly | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Coronary Artery Disease | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Myocardial Infarction | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Nervous System Disorders | 1 ( 0.3) | 2 ( 0.6) | 3 ( 0.4) | >0.9999 |
| Transient Ischaemic Attack | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.3) | >0.9999 |
| Facial Paralysis | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Gastrointestinal Disorders | 1 ( 0.3) | 1 ( 0.3) | 2 ( 0.3) | >0.9999 |
| Abdominal Discomfort | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Gastric Volvulus | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Hiatus Hernia | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Injury, Poisoning and Procedural Complications | 0 | 2 ( 0.6) | 2 ( 0.3) | 0.4993 |
| Fall | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |

Table 14.3.3.2
Number and Percentage of Subjects with Serious Adverse Events, by Treatment Group, System Organ Class, and Preferred Term
Safety Population -- All Subjects

| System Organ Class (SOC)<br>Preferred Term (PT) | Netarsudil 0.02% QD (N=351)<br>n (%) | Timolol 0.5% BID (N=357)<br>n (%) | All Subjects (N=708)<br>n (%) | p-value[1] |
|---|---|---|---|---|
| Injury, Poisoning and Procedural Complications (Cont.) | | | | |
| Radius Fracture | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Infections and Infestations | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Pneumonia | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Psychiatric Disorders | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Mental Status Changes | 0 | 1 ( 0.3) | 1 ( 0.1) | >0.9999 |
| Renal and Urinary Disorders | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Bladder Prolapse | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Reproductive System and Breast Disorders | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Cervical Dysplasia | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Respiratory, Thoracic and Mediastinal Disorders | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |
| Pneumonia Aspiration | 1 ( 0.3) | 0 | 1 ( 0.1) | 0.4958 |

*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.
n is the number of subjects with at least one adverse event in the System Organ Class or Preferred Term; % is based on the number of subjects (N) in a given treatment group for the population being analyzed.
When reporting incidence, a subject is only counted once if they ever experience an event within the System Organ Class or individual Preferred Term.
System Organ Classes and Preferred Terms within System Organ Classes are ordered by descending incidence values based on All Subjects.
System Organ Class and Preferred Term are based on Version 19.0 of the MedDRA coding dictionary.
[1] p-values are from a Fisher's exact test comparing the incidence between Netarsudil 0.02% QD vs Timolol 0.5% BID.
Listing Reference: 16.2.7.1
Source: SDC - P:\Projects\Aerie\AR-13324-CS304\Statistics\Programs\Primary Programs\TLF\t_ae3.sas 24APR2017 15:00:40

A total of 23 serious TEAEs were reported in Study AR-13324-CS304: 11 events in 8 (2%) of netarsudil QD subjects and 12 events in 10 (3%) of timolol BID subjects. No serious TEAE occurred in the Eye Disorders system organ class.

**COMMON ADVERSE EVENTS**

**Table 1 Ocular Adverse Events Reported in ≥ 2.0% of Subjects - Treatment Group (Pooled Phase 3 Safety Population)**

| SOC | Netarsudil 0.02% QD N=805 n(%) | Netarsudil 0.02% BID N=253 n (%) | Timolol 0.5% BID N=816 n (%) |
|---|---|---|---|
| **Eye Disorders** | 576 ( 71.6) | 215 ( 85.0) | 214 ( 26.2) |
| Conjunctival Hyperaemia | 428 ( 53.2) | 168 ( 66.4) | 85 ( 10.4) |
| Cornea Verticillata | 162 ( 20.1) | 64 ( 25.3) | 2 ( 0.2) |
| Conjunctival Haemorrhage | 137 ( 17.0) | 49 ( 19.4) | 15 ( 1.8) |
| Vision Blurred | 60 ( 7.5) | 44 ( 17.4) | 12 ( 1.5) |
| Lacrimation Increased | 53 ( 6.6) | 25 ( 9.9) | 5 ( 0.6) |
| Erythema of Eyelid | 52 ( 6.5) | 12 ( 4.7) | 4 ( 0.5) |
| Visual Acuity Reduced | 44 ( 5.5) | 22 ( 8.7) | 13 ( 1.6) |
| Eye Pruritus | 31 ( 3.9) | 20 ( 7.9) | 7 ( 0.9) |
| Conjunctival Oedema | 23 ( 2.9) | 19 ( 7.5) | 1 ( 0.1) |
| Eye Irritation | 31 ( 3.9) | 13 ( 5.1) | 12 ( 1.5) |
| Eyelid Oedema | 25 ( 3.1) | 12 ( 4.7) | 6 ( 0.7) |
| Foreign Body Sensation in Eyes | 21 ( 2.6) | 14 ( 5.5) | 6 ( 0.7) |
| Punctate Keratitis | 27 ( 3.4) | 12 ( 4.7) | 14 ( 1.7) |
| Conjunctivitis Allergic | 21 ( 2.6) | 11 ( 4.3) | 1 ( 0.1) |
| Eye Pain | 17 ( 2.1) | 11 ( 4.3) | 16 ( 2.0) |
| Blepharitis | 15 ( 1.9) | 8 ( 3.2) | 5 ( 0.6) |
| Corneal Opacity | 6 ( 0.7) | 11 ( 4.3) | 1 ( 0.1) |
| Eyelids Pruritus | 17 ( 2.1) | 4 ( 1.6) | 2 ( 0.2) |
| Eye Discharge | 12 ( 1.5) | 8 ( 3.2) | 6 ( 0.7) |
| Dry Eye | 17 ( 2.1) | 4 ( 1.6) | 13 ( 1.6) |
| Photophobia | 11 ( 1.4) | 8 ( 3.2) | 2 ( 0.2) |
| **General Disorders and Administration Site Conditions** | 231 ( 28.7) | 78 ( 30.8) | 220 ( 27.0) |
| Instillation Site Pain | 158 ( 19.6) | 45 ( 17.8) | 175 ( 21.4) |
| Instillation Site Erythema | 74 ( 9.2) | 32 ( 12.6) | 13 ( 1.6) |
| Instillation Site Discomfort | 23 ( 2.9) | 7 ( 2.8) | 21 ( 2.6) |
| **Investigations** | 101 ( 12.5) | 28 ( 11.1) | 79 ( 9.7) |
| Vital Dye Staining Cornea Present | 65 ( 8.1) | 17 ( 6.7) | 57 ( 7.0) |
| **Infections and Infestations** | 82 ( 10.2) | 37 (14.6) | 80 ( 9.8) |
| Conjunctivitis | 12 ( 1.5) | 8 ( 3.2) | 4 ( 0.5) |

Table includes all related and not-related events reported for ≥2.0% of subjects in any treatment group. Events are presented by SOC and PT (MedDRA Version 19.0).
**Source:** ISS Table 14.3.3.1.99.1.

The most common ocular adverse reaction observed in controlled clinical studies with netarsudil dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in netarsudil -treated patients were first noted at 4 weeks of daily dosing. This event did not result in any apparent visual functional changes in patients. Majority of corneal verticillata resolved upon discontinuation of treatment.

**Table 2 Non-Ocular Adverse Events Reported in ≥ 2.0% of Subjects - Treatment Group (Pooled Phase 3 Safety Population)**

| SOC | Netarsudil 0.02% QD N=805 n(%) | Netarsudil 0.02% BID N=253 n (%) | Timolol 0.5% BID N=816 n (%) |
|---|---|---|---|
| **Infections and Infestations** | 82 ( 10.2) | 37 ( 14.6) | 80 (9.8) |
| Upper respiratory tract infection | 15 (1.9) | 9 (3.6) | 23 (2.8) |
| Urinary Tract Infection | 8 (1.0) | 5 (2.0) | 7 (0.9) |
| **Nervous System Disorders** | 31 (3.9) | 18 (7.1) | 41 (5.0) |
| Headache | 12 (1.5) | 10 (4.0) | 15 (1.8) |
| **Skin and Subcutaneous Tissue** | 23 (2.9) | 15 (5.9) | 16 (2.0) |
| Dermatitis Allergic | 4 (0.5) | 6 (2.4) | 0 |

Table includes all related and not-related events reported for ≥2.0% of subjects in any treatment group. Events are presented by SOC and PT (MedDRA Version 19.0).
**Source:** ISS Table 14.3.3.1.99.1.

**SPECIAL SAFETY STUDIES**

## Study AR-13324-OBS01: A prospective, targeted, non-interventional (observational) study of subjects who developed corneal deposits in clinical trials AR-13324-CS301 and AR-13324-CS302

This was a targeted, prospective, multicenter, non-interventional (observational), cohort study designed to follow up and collect additional safety data in subjects who developed corneal verticillata in clinical trials AR-13324-CS301 and AR-13324-CS302.

For a very detailed description and summary, see the Medical Officer's review in DARRTS dated 11/8/2017.

This was a non-interventional observational study. Subjects were not treated with any investigational products during this observational study. They were allowed, however, to recommence or continue treatment with IOP-lowering agents or other topical ocular medications (Rx or OTC) as recommended by their eye care provider/practitioner. The previous treatment assignments in clinical trials AR-13324-CS301 and AR-13324-CS302 were to be used for the analysis. As no subjects from AR-13324-CS301 were enrolled, only subjects from AR-13324-CS302 were used for the analysis.

Corneal verticillata was reported in 16.7% (76/454) of netarsudil QD subjects and 25.3% (64/253) of netarsudil BID subjects. From the completed studies, a total of 47 subjects were enrolled in the study; however, 2 subjects, 258-018 and 258-021, were identified to have an ocular history of corneal epithelial haze at Visit 1. Corneal epithelial haze is a complicating factor for corneal verticillata and the two subjects exited the study immediately. Therefore, 45 subjects were included in the analysis reports.

At the completion of Study AR-13324-OBS01, corneal verticillata resolved in all subjects except for 3 subjects (4 out of the 6 eyes) where corneal verticillata remained stabilized but unresolved. Two of the three subjects used concomitant medications (naproxen and Advil). There was no clinically meaningful change in the visual acuity from baseline with presence of corneal verticillata to resolution/stabilization of the corneal verticillata.

**Safety Summary Statement**
In an integrated analysis of the Phase 3 studies (Studies AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304), the most common reported ocular adverse events observed with netarsudil dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Endothelial cell density was measured in AR-13324-CS302. Mean endothelial cell density in the study eye of subjects in the AR-13324 QD, BID and timolol groups was 2480, 2447 and 2455 cells/$mm^2$, respectively, at baseline and 2489, 2450, and 2451 cells/$mm^2$, respectively, at Day 90. Values were similar in the AR-13324 QD and BID groups relative to timolol at both baseline and Day 90. Similar values were reported in the fellow eyes at baseline and Day 90.

The safety database contained in this submission establishes the safety of netarsudil ophthalmic solution, 0.02% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

A risk management plan is not necessary given the adverse event profile and minimal / no systemic levels of the drug (as the drug is administered topically).

# 9. Advisory Committee Meeting

A Dermatologic and Ophthalmic Drugs Advisory Committee Meeting was held on 10/13/17 at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, Great Room (Rm. 1503), Silver Spring, Maryland.

The following two Agency questions were put to a committee vote:

**VOTE #1 :** Do the clinical trials support the efficacy of netarsudil ophthalmic solution for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension?

YES-10
NO-0
ABSTAIN-0

**VOTE #2:** Does the efficacy of netarsudil ophthalmic solution, demonstrated in the clinical trials, outweigh the safety risks identified for the drug product?

YES-9
NO-1
ABSTAIN-0

If no, what additional trials would you recommend? *One committee member suggested longer duration trials where the continued follow-up could look more closely at the side effects that have been previously identified.*

**DISCUSSION:** Please discuss any suggestions you have concerning the proposed draft labeling of the product.

Bullet point summary of discussion:

- Recommend adding corneal verticillata to Highlights section
- Using more than once per day will increase side effects
- Put actual percentages for side effects in Section 6.1
- Add peak concentration in Section 12.3
- Add in vivo description for metabolism in Section 12.3.

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# 10. Pediatrics

On 8/11/14, a final agreed upon PSP was submitted to the IND 113064. The proposal was to enroll pediatric subjects into both studies,if possible. At the completion of the studies, only two pediatric subjects, 11 and 14 years of age, were enrolled in one Phase 3 trial (AR-13324-CS302).

The product was presented at PeRC on 10/25/17. The PeRC agreed with the Division to grant a full waiver. Therefore, the product information will indicate that safety and effectiveness in pediatric patients below the age of 18 have not been established.

# 11. Other Relevant Regulatory Issues

**DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)**
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Rhopressa, and granted conditional acceptance on 5/18/2017. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional. DMEPA completed a labeling review of the originally submitted labeling on 7/13/17.

**OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)**
The Office of Prescription Drug Promotion (OPDP) completed a formal review of the substantially complete package insert on 11/15/17 and was present at the formal team labeling meetings.

**FINANCIAL DISCLOSURE**
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)**
Per the Office of Scientific Investigations review completed on 9/24/2017:

The Applicant submitted this NDA to support the use of Rhopressa for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

The clinical sites of Drs. Cooke and Logan were selected for inspection because they were among the highest domestic enrollers. Dr. Cooke has 27 INDs and a history of one inspection in 1996 (NAI). Dr. Logan has nine INDs and no history of inspection.

A sponsor inspection was conducted to assess, across sites, what quality measures were or were not in place to assure data integrity for Protocols AR-13324-CS301 and AR- 13324-CS302.

| Site #/ Name of CI/ Address | Protocol #/ # of Subjects (enrolled) | Inspection Dates | Classification |
|---|---|---|---|
| Site #125<br><br>David L. Cooke, M.D.<br>Great Lakes Eye Care<br>2848 Niles Road<br>St. Joseph, MI 49085 | AR-13324-CS301<br>Subjects: 35 | 23-29 Jun 17 | VAI<br>Pending final classification |
| Site #251<br><br>Andrew G. Logan, M.D.<br>Logan Ophthalmic Research, Inc.<br>7401 N. University Drive<br>Tamarac, FL 33321 | AR-13324-CS302<br>Subjects: 36 | 13-20 Jul 17 | VAI |
| Sponsor<br><br>Aerie Pharmaceuticals, Inc.<br>135 US Highway 206, Suite 215<br>Bedminster, NJ 07921 | AR-13324-CS301<br>AR-13324-CS302 | 21-23 Aug 17 | NAI<br>Pending final classification |

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

**Cooke, M.D.:** A Form FDA 483 was issued at the conclusion of the inspection noting that the investigation was not conducted in accordance with the investigational plan. Specifically, subjects were to have intraocular pressures (IOPs) measured at specific visits, and where two consecutive measures differed by more than 2 mm Hg, a third assessment was to be done. Subject 002 did not have IOP assessments performed at Visit 1. Subject 004 had IOPs of 17 and 20 at Visit 2 and Subject 007 had IOPs of 19 and 22 at Visit 3, but these assessments were not repeated as required by protocol for either subject.

The Form FDA 483 also noted that clinical laboratory tests at Visit 1 were to be reviewed by the clinical investigator (CI). Creatinine results were unavailable for Subject 015, and the CI noted on the laboratory test record that the creatinine was "assumed normal." Dr. Cooke responded to the Form FDA 483 in a letter dated July 7, 2017. His response was adequate.

**Logan, M.D.:** A Form FDA 483 was issued at the conclusion of the inspection noting that the CI failed to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the audited records of 18 subjects had 14 "transcription discrepancies" between the source documents and the eCRFs and another five (5) instances of information regarding adverse events or concomitant medications not captured in the eCRFs.

The 14 "transcription deficiencies" (for 11 subjects) between the source documents and eCRFs all pertained to non-serious adverse events. In particular, there was updated "action taken" and outcome information in the source documents that was not reflected in the eCRFs.

In addition, there were five (5) instances (in four subjects) of non-serious adverse events or concomitant medications that were not captured in the eCRFs and therefore not reported in the line listings. Specifically, Subject 020 experienced bradycardia, Subject 033 was administered dorzolamide, Subject 044 experienced increased glucose levels and kidney stones, and Subject 050 experienced an upper respiratory tract infection. Dr. Logan responded to the Form FDA 483 in a letter dated August 7, 2017. His response was adequate.

**Aerie:** A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

# 12. Labeling

NDA 208254 Rhopressa (netarsudil ophthalmic solution) 0.02% is recommended for approval with the attached labeling submitted 12/12/17 for reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

We concluded that presenting the analyses of the secondary endpoint of mean IOP change from baseline illustrating the results for subjects with baseline IOP <25 mmHg and subjects with baseline IOP ≥ 25 mmHg separately would be informative. A Table illustrating these results through Day 90 for all three trials is included in Section 14 of the Prescribing Information.

Corneal verticillata are described in the Adverse Reactions section of the Prescribing Information and included in the Highlights section consistent with the Advisory Committee recommendation.

# 13. Postmarketing Recommendations

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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WILLIAM M BOYD
12/14/2017

WILEY A CHAMBERS
12/14/2017

JOHN J FARLEY
12/15/2017