MA-RHO-18-002

A MULTICENTER, OPEN-LABEL STUDY OF RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) 0.02% FOR THE REDUCTION OF ELEVATED INTRAOCULAR PRESSURE IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENSION IN A REAL-WORLD SETTING

NCT03808688

18 December 2018

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MOST: Multi-center, Open-label STudy

PROTOCOL NUMBER	MA-RHO-18-002
ORIGINAL PROTOCOL DATE	18 Dec 2018
REVISED PROTOCOL DATE	N/A
INVESTIGATOR	Multiple
INSTITUTIONAL REVIEW BOARD	TBD
SPONSOR	Aerie Pharmaceuticals, Inc. 2030 Main Street, Suite 1400 Irvine, CA 92614

Aerie Clinical Protocol Approval

Role	Name	Title	Signature
Phase 4 Clinical Operations	[redacted]	[redacted]	Signature Date
Phase 4 Management	[redacted]	[redacted]	Signature Date
Aerie Senior Management	[redacted]	[redacted]	Signature Date

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INVESTIGATOR'S SIGNATURE PAGE

I agree to:

1. Implement and conduct this study diligently and in strict compliance with the protocol, Good Clinical Practice, and all applicable laws and regulations.

2. Maintain all information supplied by Aerie Pharmaceuticals, Inc. in confidence and, when this information is submitted to an Institutional Review Board, Independent Ethics Committee or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

Investigator's Title

Name of Facility

Location of Facility (City, State)

Acknowledged By:

Signature of Sponsor's Representative	Date
Printed Name and Title	Date

Fax or email signed/dated Investigator's Signature Page to [redacted].

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PERSONNEL AND FACILITIES

[redacted]

[redacted]

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1.0 BACKGROUND AND RATIONALE

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness. A major risk factor for glaucomatous visual field loss is elevated intraocular pressure (IOP; The AGIS Investigators 2000). The need for improved efficacy of glaucoma medications is supported by several clinical studies. Studies such as the Early Manifest Glaucoma Trial (Heijl 2002), the Ocular Hypertension Treatment Study (Kass 2002; Kass 2010), and the Collaborative Normal Tension Glaucoma Study Group (Collaborative Normal-Tension Glaucoma Study Group 1998) support the general conclusion that for delaying disease progression, every millimeter of reduction in IOP is significant. This conclusion holds true not only for ocular hypertensive and glaucoma patients with elevated IOPs but also for glaucoma patients with IOPs in the statistically normal range. Thus, the foundational goal for treating patients should be to lower the IOP, to the point that it prevents further damage to the optic nerve and achieve this without sacrificing safety or convenience.

Inhibitors of Rho kinase (ROCK) have emerged as a new class of IOP-lowering agents and recently, Rhopressa® (netarsudil ophthalmic solution) 0.02% was approved by the United States Food and Drug Administration for reducing elevated IOP. Three randomized and controlled clinical trials demonstrated up to 5 mmHg reductions in IOP for subjects treated with netarsudil 0.02% once daily (QD) in the evening. For subjects with baseline IOP <25 mmHg, the IOP reductions with netarsudil 0.02% dosed QD were similar to those with timolol 0.5% dosed twice daily (Rhopressa® Prescribing Information 2017).

Netarsudil 0.02% is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. Netarsudil 0.02% lowers IOP through a distinct mechanism of action: increasing trabecular outflow by decreasing acto-myosin–driven cellular contraction and reducing production of extracellular matrix proteins (Kazemi 2018; Lin 2018). In preclinical studies, netarsudil 0.02% was shown to not only increase trabecular outflow facility (Lin 2018; Wang 2015; Ren 2016; Li 2016), but also to decrease episcleral venous pressure (Kiel 2015) and aqueous humor production (Wang 2015). The mechanisms of action of netarsudil 0.02% were further explored in a phase 1 study of healthy human volunteers, in whom netarsudil 0.02% QD was demonstrated to lower IOP primarily by increasing outflow facility, but also by reducing episcleral venous pressure (Kazemi 2018).

2.0 STUDY OBJECTIVE

The objective of this study is to to evaluate the IOP lowering efficacy of netarsudil 0.02% when used as monotherapy or when used concomitantly with other IOP-lowering agents in subjects with elevated IOP due to open-angle glaucoma or ocular hypertension in a real-world clinical setting.

3.0 STUDY DESIGN

This is a multicenter, prospective, open-label study.

Subjects diagnosed with open-angle glaucoma or ocular hypertension will be evaluated at a Baseline Visit (Visit 1, Day 0). Subjects satisfying Visit 1 inclusion/exclusion criteria will be invited to participate in this study.

At the Baseline Visit (Visit 1, Day 0), all enrolled subjects will be dispensed netarsudil 0.02% and instructed to begin dosing in each eye QD in the evening. During the 12-week follow-up period, subjects will complete 2 visits (Visit 2: 6 weeks [±7 days], Visit 3: 12 weeks [±7 days]), during which IOP will be evaluated.

4.0 STUDY POPULATION

4.1 Number of Subjects

Approximately two hundred and fifty (250) male or female subjects will participate in this study.

4.2 Number of Study Centers

Approximately 32 study centers will be utilized in this study.

4.3 Subject Eligibility

To be eligible for enrollment into the study, subjects must meet all inclusion and exclusion criteria detailed in Section 4.3.1 and Section 4.3.2.

4.3.1 Inclusion Criteria

The following are criteria for inclusion in the study. Criteria required at the Baseline Visit (Visit 1, Day 0) ONLY are so indicated.

1. Male or female subjects (aged 18 or older)
2. Subjects diagnosed with open-angle glaucoma or ocular hypertension, and determined by the treating physician to require additional IOP-lowering treatment with netarsudil 0.02% either as first-line monotherapy, as a replacement of prior IOP-lowering medication, or used concomitantly with other IOP-lowering medication
3. Willingness to follow protocol requirements, including signed informed consent, routine follow-up schedule, completing questionnaires and completing laboratory tests

4.3.2 Exclusion Criteria

The following are criteria for exclusion from the study:

1. Have any active ocular disease other than glaucoma or ocular hypertension that would interfere with study interpretation
2. Women of childbearing potential who are pregnant, nursing, or planning a pregnancy and not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is 1 year post-menopausal or has a documented plasma follicle-stimulating hormone (FSH) level > 35 mIIU/mL in conjunction with hormone replacement therapy or post-surgical sterilization (see Section 7.4). Male subjects with a female partner of childbearing potential must have had a prior vasectomy or agree to use an effective method of birth control during the treatment period and for 3 months after the subject has completed the study. All women of childbearing potential must have a negative pregnancy test result at the Baseline Visit and must not intend to become pregnant during the study
3. Known sensitivity or allergy to the study medication or components
4. Any systemic disease or clinical evidence of any condition which would make the subject, in the opinion of the investigator, unsuitable for the study or could potentially confound the study results
5. Concurrent participation or prior participation in any investigational drug or device study within the last 30 days prior to the Baseline Visit

4.3.3 Subject Withdrawal Criteria

Criteria and procedures for handling subjects who are discontinued from the study are described in Section 9.2. Subjects who are discontinued will not be replaced.

5.0 STUDY MEDICATION AND OTHER STUDY SUPPLY INFORMATION

5.1 Study Medications

5.1.1 Study Medication Information

Enrolled subjects will be instructed to self-instill 1 drop of netarsudil 0.02% in each eye QD in the evening, beginning the evening of the Baseline Visit (Visit 1).

Netarsudil ophthalmic solution 0.02% will be provided by Aerie Pharmaceuticals, Inc. in the marketed containers and available for dispensing at the Baseline Visit (Visit 1, Day 0) and Visit 2 (Week 6).

Detailed information is provided in the Rhopressa Package Insert (Appendix 3).

5.1.2 Formulations

Netarsudil 0.02%

Name:	Rhopressa® (netarsudil ophthalmic solution) 0.02%
Active ingredient:	netarsudil mesylate 0.285 mg
Other ingredients:	mannitol, boric acid, sodium hydroxide to adjust pH and water for injection, benzalkonium chloride 0.15 mg (preservative)

5.1.3 Storage, Handling, Dispensing and Reconciliation of Study Medications

The study medication must be stored refrigerated at 2º to 8ºC (36º to 46ºF) at the study site in a secure area and administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in the protocol.

Store netarsudil 0.02% at 2º to 8ºC (36º to 46ºF) until opened. After opening, the product may be kept at 2º to 25ºC (36º to 77ºF) for up to 6 weeks.

Subjects are to save all used/unused bottles for presentation to designated study staff during office visits.

Study Medication Supply Records at Study Sites:

It is the responsibility of the investigator to ensure that a current record of study medication disposition is maintained. Records or logs should include:

- Amount received and placed in storage area
- Dates and initials of the person(s) responsible for each product inventory entry/movement
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area for dispensing or storage if necessary
- Non-study disposition (eg, lost, wasted, broken)

Destruction of Study Medication Supplies:

After subjects have completed study medication usage, all study medications (used and unused) will be collected by a designated staff. Only upon direction of sponsor and after reconciliation, all used/unused or undispensed study medication will be destroyed at the study site according to the site's usual medication destruction practices.

5.1.4 Site Personnel Study Medication Instructions

Subjects will be instructed to start self-administering study medication in each eye in the evening of the Baseline Visit (Visit 1) (see Section 5.1.5 below). There is no washout period required for subjects replacing prior IOP-lowering therapy with netarsudil ophthalmic solution 0.02%.

Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses before instillation of study medication and not place them in their eye(s) until 15 minutes after instillation.

If netarsudi 0.02% is to be used concomitantly with other topical ophthalmic drug products to lower IOP, each drug product should be administered at least 5 minutes apart to prevent washout.

5.1.5 Subject Dosing and Storage Instructions (Visits 1 & 2)

Baseline Visit (Visit 1) and Follow-Up Visit 2

Visit 1 Study Medication Dosing Instructions

Enrolled subjects will receive 2 bottles of netarsudil 0.02% at the Baseline Visit (Visit 1) and will be instructed to refrigerate both the unopened bottles (2º to 8ºC [36º to 46ºF]).

[redacted]

Subjects will return to clinic as instructed by clinic site staff for Visit 2 (Week 6) with all used/unused study medication bottles.

Visit 2 Study Medication Dosing Instructions

Subjects will receive 2 bottles of netarsudil 0.02% at Visit 2 (Week 6) and will be instructed to refrigerate both the unopened bottles (2º to 8ºC [36º to 46ºF]).

[redacted]

Subjects will return to clinic as instructed by clinic site staff for Visit 3 (Week 12) with all used/unused study medication bottles.

5.2 Additional Study Supplies

The following supplies will be provided to the study site:

- Combined Informed Consent/ Health Insurance Portability and Accountability Act of 1996 (HIPAA) form, as applicable per Institutional Review Board (IRB)
- Screening and Enrollment logs
- Electronic case report form (eCRF) completion guidelines
- Study medication reconciliation logs

- Package insert for Rhopressa (netarsudil ophthalmic solution) 0.02%

6.0 PRIOR AND CONCOMITANT THERAPIES

6.1 Allowed Medications or Treatments

Therapy considered necessary for a subject's welfare will be given at the discretion of the investigator and documented during the course of the study. The use of any concurrent medication (prescription or over-the-counter, including herbal medications) is to be recorded in a subject's source documentation (charts), as well as in the case report forms (CRFs), noting the date, dosage, frequency, start date, and reason for taking the medication(s).

7.0 STUDY PROCEDURES

7.1 Subject Entry Procedures

7.1.1 Overview of Entry Procedures

Subjects meeting inclusion and exclusion criteria (Section 4.3.1 and Section 4.3.2, respectively) will be considered for enrollment in this study. [redacted]

7.1.2 Informed Consent and HIPAA Authorization

Subjects meeting enrollment criteria at the Baseline Visit (Visit 1) will be asked to participate in the study. The study design, follow-up, and participation parameters/criteria will be discussed with each subject. Subjects wishing to participate must provide written informed consent and sign an "Authorization for Use and Disclosure of Health Information for Research" release as a component of the informed consent document (HIPAA authorization) prior to any study-related procedures.

7.1.3 Method for Assignment of Subject ID Number

[redacted]

7.2 Study Procedures

The Schedule of Visits/Procedures for this study is included in Appendix 4.

Clinical assessments will be performed throughout the study as detailed in Section 8.0. All clinical assessments will be performed by the investigator (or designee).

7.3 Overall Instructions

Evaluations should be performed by the same evaluator throughout the study whenever possible. If this is not possible, 2 evaluators should assess the same subject simultaneously and reach agreement on results.

7.4 Visit 1 (Day 0): Baseline

The investigator (or designee) will perform/administer the following assessments:

- Written informed consent and HIPAA authorization
- Demographics

- Subject eligibility (inclusion/exclusion criteria)
- Urine pregnancy test (if applicable)
- Medical and IOP history
- Prior and concomitant medications and/or procedures review
- Best-corrected visual acuity (BCVA)
- Biomicroscopy
- IOP assessment (measured in each eye using Goldmann applanation tonometer)
- Blood pressure measurement (sitting position)
- Corneal pachymetry to measure central corneal thickness
- Assign subject ID number
- Dispense netarsudil 0.02% and have a staff member instruct the subject on use
- Schedule Visit 2 (Week 6)

Women of childbearing potential* must be willing to practice medically effective contraception for the duration of the study (ie, abstinence, condoms or diaphragm with spermicide, intrauterine device (IUD), or birth control pills) and must not be lactating.

**A woman of childbearing potential is one who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy), or is not postmenopausal. Postmenopausal is defined as amenorrhea for at least 12 consecutive months or a documented plasma FSH level >35 mIU/mL in conjunction with hormone replacement therapy. Women who are using oral, implanted, skin patches, or injectable contraceptive hormones, an IUD, or barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, practicing abstinence, or where partner is sterile (eg, vasectomy), are considered to be of childbearing potential.*

7.5 Visit 2 (Week 6): Follow-Up

The investigator (or designee) will perform/administer the following assessments:

- Concomitant medications and/or procedures review
- BCVA
- Biomicroscopy
- IOP assessment (measured in each eye using Goldmann applanation tonometer)
- Blood pressure measurement (sitting position)
- Adverse event (AE) assessment
- Collect used/unused study medication containers
- Dispense netarsudil 0.02% and have a staff member instruct the subject on use
- Schedule subject's next visit (Visit 3, Week 12)

7.6 Visit 3 (Week 12): Final Visit

The investigator (or designee) will perform/administer the following assessments:

- Concomitant medications and/or procedures review

- BCVA
- Biomicroscopy
- IOP assessment (measured in each eye using Goldmann applanation tonometer)
- Blood pressure measurement (sitting position)
- [redacted] Questionnaire
- [redacted] Questionnaire
- AE assessment
- Collect used/unused study medication containers
- Complete End of Study (Exit) Form

7.7 Unscheduled Visits

In the event a subject returns for an unscheduled visit, the investigator (or designee) will perform/administer necessary assessments. Information collected from an unscheduled visit will be reported on Interim/Unscheduled Visit CRF(s).

8.0 CLINICAL ASSESSMENTS

The following clinical assessments will be performed according to the schedule as indicated in the Schedule of Visits/Procedures (Appendix 4). The same investigator (or designee) should complete the evaluations for a given subject throughout the study.

8.1 Efficacy Assessment

8.1.1 Intraocular Pressure

IOP will be measured in both eyes using a Goldmann applanation tonometer affixed to a slit lamp at the Baseline Visit, Visit 2, and Visit 3.

8.2 Safety Assessments

8.2.1 Adverse Events

At both Visit 2 (Week 6) and Visit 3 (Week 12) the investigator (or designee) will question each subject regarding adverse experiences that may have occurred since a previous visit. Subjects will be queried “How are you feeling?” and all AEs will be recorded in the CRFs including severity, action taken, and relationship to the study medication(s) (see Section 10.0 for further details).

Please see “Rhopressa Package Insert” (Appendix 3) for further details regarding possible adverse experiences associated with the use of study medication.

8.2.2 Best Corrected Visual Acuity

BCVA will be measured for both eyes by the investigator (or designee) at the Baseline Visit (Visit 1) and at both Visit 2 (Week 6) and Visit 3 (Week 12) using a Snellen Visual Acuity Chart (see Appendix 5 for detailed information on this examination).

8.2.3 Biomicroscopy

Biomicroscopy will be performed by the investigator (or designee) for both eyes at the Baseline Visit and at each follow-up visit by slit lamp examination without pupil dilation. Eye structures/surfaces to be assessed include, but are not limited to,

lids/lashes, conjunctiva (palpebral and bulbar), cornea, anterior chamber and lens. All observations will be recorded. (see Appendix 5 for detailed information on this examination).

8.2.3 Pregnancy Testing

A urine human chorionic gonadotropin (hCG) pregnancy test (only for females who are not diagnosed as postmenopausal or surgically sterile) will be used in this study and performed at the Baseline Visit to immediately confirm non-pregnancy eligibility for women of child-bearing potential.

The investigator must immediately notify the Ethics Committee/IRB and Aerie, of any pregnancy associated with the study medication exposure and keep careful source documentation of the event. In addition, the investigator must complete the pregnancy surveillance form(s) to ensure all required information is reported.

8.2.4 Blood Pressure Measurement

Systemic safety assessment measured by the investigator (or designee) at the Baseline Visit (Visit 1) and at Visit 2 (Week 6) and Visit 3 (Week 12).

8.3 Other Assessments

8.3.1 [redacted] Questionnaire

An [redacted] Questionnaire (see Appendix 1 for detailed information on this questionnaire) will be administered by the investigator (or designee) at Visit 3 (Week 12).

8.3.2 [redacted] Questionnaire

At Visit 3 (Week 12), the investigator will complete a [redacted] Questionnaire (see Appendix 2 for detailed information on this questionnaire).

9.0 END OF STUDY

At the end of each subject's participation in the study, the investigator (or designee) will complete an End of Study Form (Completion) for all completed and discontinued subjects.

9.1 Completion of the Study

Each subject who completes the entire Schedule of Visits as specified in this protocol will have completed the study.

9.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any reason and categorized as follows:

- AEs
- Lost to follow-up
- Other (administrative reasons, etc.)

If a subject discontinues from the study for any reason at any point beyond his/her Baseline Visit (Visit 1), he/she should be requested to return for a final visit at which time all Visit 3 (Week 12) procedures should be performed according to the protocol Schedule of Visits/Procedures (see Appendix 4).

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

9.3 Study Termination

The study may be terminated by the investigator or the sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, the investigator may stop the study. Study termination by the investigator will be reported to the sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the sponsor and the IRB by the investigator within 5 working days.

In the event that the sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

10.0 ADVERSE EVENT DEFINITIONS AND REPORTING

10.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject during the course of a study. An AE can, therefore, be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational or marketed medicinal product, whether or not considered related to the investigational or marketed medicinal product. AEs include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study medication(s) under study.

Study medication is defined as a pharmaceutical form of an active ingredient or vehicle/placebo being tested or used as a reference in the study, whether masked or unmasked. AEs may be either spontaneously reported or elicited during questioning and examination of a subject.

All AEs must be completely recorded on the appropriate AE form. The severity of each AE will be graded by the investigator, using the definitions in Section 10.1.1. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of study medication, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up, as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study, particularly if the AE was considered by the investigator to be related, or possibly/unlikely related to investigational product.

AEs should be followed to resolution or stabilization and reported as serious adverse events (SAEs) if they become serious (Section 10.2).

10.1.1 Severity of Adverse Events

The severity of AEs will be graded by the investigator using the following definitions:

Mild: The AE is noticeable by the subject but does not interfere in a significant manner with the subject's normal functioning and is not sufficiently intense to result in medication dose reduction or discontinuation of treatment; remedial therapy may be given.

Moderate: The AE is sufficiently intense to produce some impairment of functioning and may require a reduction in medication dose or discontinuation of treatment; remedial therapy may be given.

Severe: The AE produced a significant impairment of functioning or incapacitation and may require a reduction in medication dose or discontinuation of treatment; therapy is needed.

10.1.2 Relationship of Adverse Events

The relationship of the AE(s) to the study medication(s) must be specified by the investigator using the following definitions:

Not Related: The event is clearly related to other factors, such as subject's clinical condition, therapeutic interventions, concomitant disease, or therapy administered to the subject and does not follow a known response pattern to the product.

Unlikely Related: The event is most probably caused by other etiologies. such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.

Possibly Related: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication but could have been produced by other factors, such as the subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject.

Related: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors, such as subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject and either occurs immediately following study medication administration, improves on stopping the study medication, reappears on repeat exposure, or there is a positive reaction at the application site.

10.2 Serious Adverse Events

SAEs or reactions are any untoward medical occurrence that, at any dose, meets one or more of the following criteria:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require non-surgical or surgical intervention to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

NOTE: Aerie considers all cancer AEs as SAEs.

Investigators must record all SAEs using the appropriate CRFs.

All SAEs, whether related or unrelated to study medication, must also be immediately reported by investigators to [redacted] using one of the following mechanisms within 24 hours of learning of the event:

- **Email:** [redacted]
- **Phone Hotline:** [redacted]
- **Fax:** [redacted]

In addition, the governing Ethics Committee/IRB and Aerie Pharmaceuticals, Inc. (sponsor) must also be notified by telephone or confirmed facsimile transmission should an SAE occur.

If only limited information is initially available, follow-up reports are required. Documentation of all SAEs must be maintained in the study files – eg, Serious Adverse Event Form or equivalent form (eg, MedWatch Form). Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study medication, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to the Ethics Committee/IRB. Aerie will report any SAEs/serious adverse device effects to other investigators, relevant competent authorities, and Ethics Committee/IRB, as required by local health care authorities.

The investigator(s) should always group signs and symptoms into a single term that constitutes a single unifying diagnosis. The investigator's opinion of the relationship of the SAE to study medication, the duration, intensity, frequency, serious criteria, countermeasures taken with study medication, and the outcome of the SAE should be documented.

10.3 Pregnancy

Sexually active women of child bearing potential (See Section 7.4 for definition of women of childbearing potential) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

During the study, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period). If pregnancy is suspected in any female subject while the subject is receiving study treatment, the study medication must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study therapy will be permanently discontinued and the subject will be withdrawn from the trial. Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies).

The investigator must immediately notify the Ethics Committee/IRB and Aerie, of any pregnancy associated with the study medication exposure and keep careful source documentation of the event. In addition, the investigator must complete the pregnancy surveillance form(s) to ensure all required information is reported.

11.0 STATISTICAL CONSIDERATIONS

11.1 Sample Size

The planned enrollment is approximately 250 subjects.

11.2 Analysis Populations

An intent-to-treat (ITT) population will include all subjects who were enrolled into the study.

A modified intent-to-treat (mITT) population will include all subjects who were treated and had at least 1 follow-up visit with a completed IOP measurement.

A per-protocol (PP) population will include all subjects who completed 3 months of treatment without significant protocol violations. Subjects to be excluded from the PP analysis are subjects who have: 1) no efficacy evaluation at baseline, and/or have no follow-up visit; 2) used any prohibited medications during the study period that would interfere with the study objectives; 3) had any prohibited procedures during the study period that would interfere with the study objectives.

A safety population will include all subjects who have received at least 1 dose of study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

11.3 Statistical Methods

Summary tables (descriptive statistics and/or frequency distributions) will be provided for all baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, standard deviation, range, and median). Frequency distributions (counts and percentage) of subjects within each category will be provided for categorical data. Additional analyses may be conducted as described in the Statistical Analysis Plan (SAP). The SAP will be finalized and approved prior to database lock.

11.3.1 Baseline Analyses

Demographic variables (age, sex, race, etc.) will be summarized by treatment group for analysis population.

Baseline characteristics (as recorded on the eCRF) will be summarized by treatment group for analysis population.

11.3.2 Efficacy Analysis

Efficacy data will be analyzed using ITT (with and without imputation of missing Week 12 assessments), mITT (without imputation of missing values), and PP populations (without imputation of missing values). No imputation will be performed for missing Week 6 values. Imputation for missing Week 12 values will be performed using the method of last observation carried forward from Week 6.

Efficacy data will be evaluated for overall, monotherapy. and concomitant participant groups.

11.3.2.1 IOP

If both eyes qualify for study inclusion, analyses will be provided for the worse eye at baseline. If both study eyes are the same at baseline, then data for only the right eye will be analyzed.

The primary efficacy variable is percent reduction from baseline IOP.

11.3.3 Safety Analyses

Safety data will be summarized for the Safety population.

11.3.3.1 Adverse Events

All treatment-emergent AEs/SAEs will be summarized with frequency distributions by treatment group, system organ class, and preferred term using version 21.1 of the Medical Dictionary for Regulatory Activities (MedDRA) as well as by ocular versus non-ocular. Specific AEs/SAEs occurring with a frequency of 5% or more will be summarized in a separate listing.

Descriptive statistics will also be provided as data summaries.

11.3.3.2 Other Safety Assessments

Other safety variables (as recorded on the eCRF) will be either summarized or listed based on the frequency.

11.3.4 Other Assessments

[redacted]

11.4 Interim Analysis

No interim analyses are planned.

12.0 ADMINISTRATIVE CONSIDERATIONS

12.1 Protection of Human Subjects

12.1.1 Informed Consent Regulations

Written informed consent is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative.

12.1.2 Ethics Committee and Independent Review Board Regulations

This study is to be conducted in accordance with Ethics Committee/IRB regulations. The investigator must obtain approval from a properly constituted Ethics Committee/IRB prior to initiating the study and re-approval or review at least annually. Aerie is to be notified immediately if the responsible Ethics Committee/IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all Ethics Committee/IRB correspondence with the investigator should be provided to Aerie.

12.1.3 Good Clinical Practice Regulations

This protocol is to be conducted in accordance with the applicable Good Clinical Practice regulations and guidelines.

12.2 Changes to Protocol

The investigator should not implement any deviation from or changes to the protocol without approval by Aerie and prior review and documented approval/favorable opinion from the Ethics Committee/IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change of telephone numbers, etc.).

12.3 Quality Control and Assurance

The progress of this study will be monitored by on-site, written, and telephone communications between personnel at the investigator's site and the study monitor. The investigator will allow the sponsor or designee to inspect all documents pertinent to the study, including but not limited to: CRFs, subject records (source documents), signed informed consents, records of study medication receipt, storage and disposition and regulatory files related to the study.

12.4 Subject Confidentiality

Written authorization is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, HIPAA).

12.5 Required Study Documents

The investigator will maintain documentation demonstrating Ethics Committee/IRB approval of the study protocol and informed consent at his/her study site.

The investigator is responsible for ensuring that data are properly recorded on each subject's CRFs and related documents. The CRFs are to be submitted in a timely manner and according to an Aerie-specified schedule.

12.6 Record Retention

The investigator must maintain records related to this study for a minimum of 3 years after study completion.

13.0 REFERENCES

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APPENDIX 1: [redacted] QUESTIONNAIRE

Administered by the investigator (or designee)

Subject I.D. _____
Study Site: _____
Date Completed: _____/_____/_____
Month/Day/Year

1. [redacted]

APPENDIX 2: [redacted] QUESTIONNAIRE

Subject I.D. _____
Study Site: _____
Date Completed: _____/_____/_____
Month/Day/Year

[redacted]

APPENDIX 3: STUDY MEDICATION PACKAGE INSERT

Package Insert for Rhopressa (netarsudil ophthalmic solution) 0.02% will be supplied separately to each study site.

APPENDIX 4: SCHEDULE OF VISITS/PROCEDURES

Procedure / Visit number / Visit Window	1 Baseline (Day 0)	2 Follow-Up (Week 6) ±7 days	3 Final (Week 12) ±7 days
Informed consent & HIPAA authorization	X		
Demographics	X		
Subject eligibility (inclusion/exclusion)[1]	X		
Urine pregnancy test[2]	(X)		
Medical and IOP history	X		
Prior and concomitant medications and/or procedures review/changes	X	X	X
BCVA[3]	X	X	X
Biomicroscopy	X	X	X
IOP measurement[4]	X	X	X
Blood pressure measurement[5]	X	X	X
Pachymetry	X		
AE assessment		X	X
[redacted] Questionnaire[6]			X
[redacted] Questionnaire[7]			X
Dispense study medication bottles	X	X	
Collect used/unused study medication bottles		X	X

X = required, (X) = only if needed.

1. Women of childbearing potential must be willing to practice effective contraception for the duration of this study.
2. Female subjects only (if applicable).
3. Assessed using Snellen logarithmic visual acuity chart.
4. Assessed using Goldmann applanation tonometer affixed to a slit lamp. IOP must be measured following completion of the biomicroscopic examination.
5. Measured after the subject has been at rest in a sitting position for 5 minutes.
6. To be administered by the investigator (or designee).
7. To be completed by the investigator (or designee).

APPENDIX 5: EXAMINATION PROCEDURES

1. Best Corrected Visual Acuity

At all study visits, BCVA will be assessed in both eyes of each subject using a logarithmic visual acuity chart (Snellen or equivalent) at a distance of 12 feet.

Ensure subject is seated in a position whereby his/her eyes are 12 feet from the chart, which is hung on the wall at eye level. Mark a spot on the floor with a piece of tape to ensure subjects are seated in the exact same position every time they take the test. Also ensure subject is fitted with appropriate lenses as to provide “best correction” each time he/she takes the test. In order to standardize the conditions of the test as much as possible, all visual acuity testing should be performed in the same room under the same lighting conditions for every subject.

Perform the test on the right eye first. Ask the subject to read each letter, line by line, left to right beginning with line #1 on the top of the chart. Subjects should be told that the chart contains only letters, not numbers. If the subject reads a number, he/she should be instructed that the chart only contains letters and for him/her to “try again.” Subjects should be asked to read the letters slowly as to achieve best identification of each letter. There is no time limit for this test. Subjects are not to proceed to the next letter (or line) until they have given a finite answer.

If a subject changes a response (eg, that should be a “C” not an “O”) before he/she has read the next letter, the change will be accepted. If the subject attempts to change a response after reading the next letter in the series, the change will not be accepted.

When the letters become difficult to read or if the subject identifies a letter as 1 of 2 letters, he/she should be instructed to choose 1 letter and, if necessary, to guess. The examiner should consider the lowest line read with no more than 1 mistake as the extent of a subject’s visual acuity. This visual acuity should then be recorded (in Snellen equivalent units, eg, 20/80) on the appropriate CRF.

Repeat for the left eye.

2. Biomicroscopy

Any findings from the gross examination will be recorded in this section on the CRF. Slit lamp biomicroscopy without fluorescein and without dilation of the pupil will be performed during the study (fluorescein may be used if corneal erosion is suspected). Observations for the slit lamp biomicroscopy examination will be graded as follows:

Lids/Lashes (upper and lower)

Erythema

Rating	Score	Description
None	0	Normal, without redness
Trace	+0.5	Minimal flush reddish color, confined to a small region
Mild	+1	A flush reddish color, confined to a small region
Moderate	+2	Diffused reddish color encompassing the entire lid margin
Severe	+3	Deep diffuse reddish color of lid margins and superior or inferior eye lid

Edema

Rating	Score	Description
None	0	Normal. No swelling of the eyelid tissue

Trace	+0.5	Minimal swelling of the lids, above normal, which is regional
Mild	+1	Slight swelling of the lids, above normal, which is regional
Moderate	+2	General swelling
Severe	+3	Extensive swelling of the eyelids, with or without eversion of upper and/or lower lids

Conjunctiva (Palpebral and Bulbar)

Hyperemia

Rating	Score	Description
None	0	Normal. May appear blanched to reddish-pink without perilimbal injection. Vessels of palpebral or bulbar conjunctiva easily observed
Trace	+0.5	Minimal flush, reddish color predominantly confined to the palpebral or bulbar conjunctiva
Mild	+1	A flush, reddish color predominantly confined to the palpebral or bulbar conjunctiva
Moderate	+2	Bright red color of the palpebral or bulbar conjunctiva
Severe	+3	Deep, bright diffuse redness of the palpebral or bulbar conjunctiva

Edema

Rating	Score	Description
None	0	Normal. No swelling of the conjunctiva
Trace	+0.5	Minimal swelling of the conjunctiva, above normal, which is regional
Mild	+1	Mild swelling of the conjunctiva, above normal, which is regional
Moderate	+2	General swelling of the conjunctiva
Severe	+3	Extensive swelling of the conjunctiva

Follicles

Rating	Score	Description
None	0	No follicles
Trace	+0.5	Minimal number of elevated follicles, with minimal surrounding vasculature
Mild	+1	Few elevated follicles with minimal surrounding vasculature
Moderate	+2	Multiple elevated follicles with moderate surrounding vasculature
Severe	+3	Elevated follicles which may involve the entire conjunctiva, with engorged vasculature

Cornea

Edema

Rating	Score	Description
None	0	No edema
Trace	+0.5	Localized, minimal (trace) epithelial haze
Mild	+1	Dull glass appearance of epithelium that may include fine localized microcystic changes
Moderate	+2	Dull glass appearance of epithelium with large number of cystic changes with or without stromal edema
Severe	+3	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Staining/Erosion

Rating	Score	Description
None	0	No erosion
Trace	+0.5	Minimal fluorescein staining confined to small focus
Mild	+1	Slight fluorescein staining confined to small focus
Moderate	+2	Regionally dense fluorescein staining (1 mm or greater in diameter) with underlying structure moderately visible
Severe	+3	Marked fluorescein staining or epithelial loss

Anterior Chamber

For the measurements of cells and flare the following settings should be used:

• 1x1 mm slit • Highest slit lamp voltage • Illumination angle of 45 degrees	• High magnification • Low ambient lighting • Same grader and slit lamp whenever possible

Cells

Rating	Score	Description
None	0	No cells seen
Trace	+0.5	1-5 cells seen
Mild	+1	6-25 cells seen
Moderate	+2	26-50 calls seen
Severe	+3	Too many cells to count

Flare

Rating	Score	Description
None	0	No Tyndall effect
Trace	+0.5	Tyndall effect barely discernible
Mild	+1	Tyndall beam in the anterior chamber has a mild intensity
Moderate	+2	Tyndall beam in the anterior chamber has a moderate-strong intensity
Severe	+3	Tyndall beam is very intense, and the aqueous has a white and milky appearance

Lens Status

Lens status will be described by the observer as phakic, pseudophakic or aphakic.

Lens Appearance (phakic eyes only)

Rating	Score	Description
None	0	No cataract
Trace	+0.5	Trace lens opacity
Mild	+1	Early lens opacity
Moderate	+2	Intermediate lens opacity
Severe	+3	Advanced lens opacity

3. Intraocular Pressure

NOTE: The examination procedure described below are to be completed for both eyes.

IOP should be measured by the study coordinator (or designee) in each eye using a Goldmann applanation tonometer affixed to a slit lamp. Measurements will be recorded on an appropriate CRF.

Please ensure tight-fitting neck wear has been loosened prior to initiating the examination. Both eyes will be tested, with the right eye preceding the left.

Instill 1 drop of topical anesthetic (eg, Ophthetic®) into each eye and wait 4 minutes before continuing with the test procedure.

Test Procedure:

1. With the subject seated, both he/she and the slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining.
2. Look through the binocular viewer of the slit lamp at low power making sure the tension knob is pre-set to the low-pressure value (4-6 mmHg).
3. Follow the image of the fluorescein-stained semicircles while rotating the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle.
4. When this image is reached, remove your fingers from the tension knob and record the IOP reading along with the time of day in the CRF.

Please note:

- IOP readings should not be adjusted for corneal thickness.
- The tonometer should be calibrated prior to or at the Baseline Visit (Visit 1) and calibration should be documented.

4. Blood Pressure

Resting state blood pressure will be measured after the subject has been seated quietly for at least 5 minutes. Blood pressure will be measured with a sphygmomanometer with appropriate size cuff and a stethoscope or with a measurement device.

5. Pregnancy Testing

A urine human chorionic gonadotropin (hCG) pregnancy test (only for females who are not diagnosed as postmenopausal or surgically sterile) will be used in this study and performed at the Baseline Visit to immediately confirm non-pregnancy eligibility for women of childbearing potential.

6. [redacted] Questionnaire

The investigator (or designee) will administer the [redacted] Questionnaire and record the subject's responses on the appropriate CRF at Visit 3 (Week 12).

7. [redacted] Questionnaire

The investigator will complete the [redacted] Questionnaire at Visit 3 (Week 12) for all subjects who complete the study.

8. Adverse Events

At both Visit 2 (Week 6) and Visit 3 (Week 12), the investigator (or designee) will question each subject regarding adverse experiences that may have occurred since a previous visit. Subjects will be queried "How are you feeling?" and all AEs will be recorded in the CRFs, including severity, action taken, and relationship to study medication.