

A Double-Masked, Randomized, Placebo-Controlled Study of Trabecular Outflow Facility Following Treatment with Netarsudil Ophthalmic Solution 0.02% (AR-13324) in Subjects with Elevated Intraocular Pressure

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### Clinical Study Protocol:

**Study Title:** AR-13324-CS206: A Double-Masked, Randomized, Placebo-Controlled Study of Trabecular Outflow Facility Following Treatment with Netarsudil Ophthalmic Solution 0.02% (AR-13324) in Subjects with Elevated Intraocular Pressure

**Study Number:** AR-13324-CS206

**Study Phase:** 2

**Product Name:** Netarsudil (AR-13324) 0.02% ophthalmic solution

**Indication:** Elevated intraocular pressure

**Investigators:** Multi-center

**Sponsor:** Aerie Pharmaceuticals, Inc.

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**Medical Monitor:** [REDACTED]

	Date
<b>Original Protocol (Rev 0):</b>	10 May 2017
<b>Amendment 1 (Rev 1):</b>	16 August 2017

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**Protocol Title: AR-13324-CS206: A Double-Masked, Randomized, Placebo-Controlled Study of Trabecular Outflow Facility Following Treatment with Netarsudil Ophthalmic Solution 0.02% (AR-13324) in Subjects with Elevated Intraocular Pressure**

**Study No: AR-13324-CS206**

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- Section 7.1 Screening Visit (Visit 1)

[REDACTED]

## SYNOPSIS

<b>Sponsor:</b> Aerie Pharmaceuticals, Inc.
<b>Name of Finished Product:</b> Netarsudil Ophthalmic Solution 0.02%
<b>Name of Active Ingredients:</b> Netarsudil mesylate (AR-13324)
<b>Study Title:</b> A Double-Masked, Randomized, Placebo-Controlled Study of Trabecular Outflow Facility Following Treatment with Netarsudil Ophthalmic Solution 0.02% (AR-13324) in Subjects with Elevated Intraocular Pressure
<b>Study Number:</b> AR-13324-CS206
<b>Study Phase:</b> 2
<b>Primary Objective:</b> To evaluate the effect on trabecular outflow facility of netarsudil ophthalmic solution 0.02% compared to placebo
<b>Secondary Objective(s):</b> To evaluate the effect on intraocular pressure (IOP) and episcleral venous pressure (EVP) of netarsudil ophthalmic solution 0.02% compared to placebo To evaluate the ocular and systemic safety of netarsudil ophthalmic solution 0.02%
<b>Study Design:</b> <p>This will be a double-masked, placebo-controlled, paired-comparison study conducted at approximately 2 centers in the US to evaluate the effect of treatment with netarsudil ophthalmic solution 0.02% (netarsudil) on trabecular outflow facility. Netarsudil will be administered to one eye and Placebo to the contralateral eye once daily, 1 drop in the morning (QD, AM), in adult subjects at least 18 years of age with primary open angle glaucoma (POAG) or ocular hypertension (OHT). Study medication will be administered for 7 consecutive days, although the total time of subject participation in the study (including washout from prior treatment, if necessary) may be up to 7 weeks.</p> <p>Subjects will be eligible to enroll in the study if they have a current diagnosis of POAG or OHT in both eyes (POAG in one eye and OHT in the contralateral eye is also acceptable), and may be treatment-naïve or taking topical ocular hypotensive medication. If necessary, subjects who agree to participate in the study will be required to washout from their current IOP-lowering treatment for a minimum specified period of time (5 days to at least 4 weeks), according to the type of treatment. Subjects will attend a total of 3 study visits: a screening visit (Visit 1), to be conducted up to 6 weeks prior to a qualification visit (Visit 2, Day 1, baseline), and a final visit after 6 days on-treatment (Visit 3, Day 8, exit) where a member of the site staff will administer their 7th dose after completing their 08:00 hour assessments.</p> <p>Both eyes must qualify for the study with an unmedicated (post-washout or treatment-naïve) IOP of &gt;20 mmHg but &lt;30 mmHg at 08:00 hours and &gt;17 mmHg but &lt;30 mmHg at 13:00 and 16:00 hours at the qualification visit. In order to be randomized into the study, eligible subjects must meet all of the inclusion, and none of the exclusion criteria at both the screening and at the qualification visit, following washout from their current ocular hypotensive treatment, if required.</p> <p>If the subject continues to be eligible, they will be randomized at the end of their qualification visit (Visit 2, Day 1, baseline) to receive netarsudil ophthalmic solution 0.02% in one eye and placebo in the contralateral eye for 7 days, QD (AM). Subjects will be randomized as to which eye will receive netarsudil ophthalmic solution</p>

0.02% and which eye will receive netarsudil ophthalmic solution placebo. Subjects will be asked to begin self-administration of their assigned medications in the morning on Day 2 following their baseline (Day 1) visit. Subjects will be instructed to administer 1 drop from each bottle of their study medication into the assigned eye for that bottle, every morning at approximately the same time (between 08:00 and 10:00 hours) for 6 consecutive days. On the day of the final (exit) visit (Visit 3, Day 8), subjects will return to the site at 08:00 hours for their final dose of study medication and to complete their on-treatment measurements before exiting.

Safety measures (including visual acuity, biomicroscopy, and adverse events) will be evaluated at all visits. Efficacy assessments will include IOP at 08:00, 13:00 and 16:00 hours, and trabecular (tonographic) outflow facility and EVP, which will be measured at 13:00 and 16:00 hours. Tonographic outflow facility (primary endpoint) and IOP (secondary endpoint) will be collected in all subjects. The other secondary endpoint, EVP, will be measured in a subset of subjects.

**Diagnosis and Main Criteria for Inclusion:**

**Key Inclusion Criteria**

Subjects have to meet all of the following criteria at screening and qualification visits to enter into the study:

1. Must be 18 years of age or older
2. Diagnosis of POAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye is acceptable)
3. Unmedicated (post-washout, or treatment-naive) IOP >20 mmHg and <30 mmHg in both eyes at 08:00 hours, and >17 mmHg but <30 mmHg at 13:00 and 16:00 hours at the qualification (Day 1, baseline) visit
4. Corrected visual acuity in each eye +1.0 on the logarithm of minimum angle of resolution (logMAR) scale or better by early treatment diabetic retinopathy study (ETDRS) chart or its equivalent in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye)
5. Be able and willing to provide signed informed consent and follow study instructions

**Key Exclusion Criteria**

Subjects meeting any of the following criteria during screening or qualification evaluations (e.g., at the time of randomization) will be excluded from entry into the study:

Ophthalmic:

1. Clinically significant ocular disease (eg, corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications for one month is not judged to be safe by the Investigator
2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (as assessed by the Investigator, e.g. Grade 2 or less, Shaffer Scale). Note: Previous laser peripheral iridotomy is NOT acceptable
3. Intraocular pressure  $\geq 30$  mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification)
4. A difference in IOP between eyes >4 mmHg (unmedicated) at any baseline time point
5. Use of more than two ocular hypotensive medications within 30 days of screening. Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as two medications
6. Known hypersensitivity to any component of the formulation (e.g., benzalkonium chloride, etc.), or to topical anesthetic.
7. Previous glaucoma intraocular surgery or glaucoma laser procedures in either eye
8. Keratorefractive surgery in either eye (e.g., radial keratotomy, PRK, LASIK, corneal cross-linking, etc.)
9. Report of ocular trauma in either eye within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the three months prior to screening
10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or zoster keratitis in either eye at

<p>screening.</p> <p>11. Use of ocular medication in either eye of any kind within 30 days of screening, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after screening), or c) lubricating drops for dry eye (which may be used throughout the study)</p> <p>12. Mean central corneal thickness greater than 620 <math>\mu\text{m}</math> in either eye at screening</p> <p>13. Any abnormality preventing reliable applanation tonometry of either eye (e.g., keratoconus, etc.)</p> <p>14. Lack of suitable episcleral vein prior to performing EVP measurement at Visit 2/Day 1 (applicable to 1 site only) [REDACTED]</p> <p><u>Systemic:</u></p> <p>15. Clinically significant abnormalities (as determined by the Investigator) in any recent (within 6 weeks prior to screening) laboratory tests which may affect the study results. Laboratory assessments, other than pregnancy tests in females of child-bearing potential and vital signs, will not be conducted for this study</p> <p>16. Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study</p> <p>17. Participation in any investigational (interventional) study within 60 days prior to screening</p> <p>18. Changes of systemic medication that could have an effect on IOP within 30 days prior to screening, or anticipated during the study, including use of any steroid-containing drug regardless of route of systemic administration (e.g., steroid inhalers)</p> <p>19. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative pregnancy test result at the screening examination and must not intend to become pregnant during the study</p>
<p><b>Study Population:</b> Approximately 20 subjects will be randomized</p>
<p><b>Investigational Product, Dose, and Mode of Administration:</b> Netarsudil ophthalmic solution 0.02%, 1 drop daily, in the morning (QD AM), topical ocular</p>
<p><b>Duration of Treatment:</b> 7 days</p>
<p><b>Efficacy Assessments:</b> The principal efficacy assessments of this study pertain to aqueous humor dynamics:</p> <ul style="list-style-type: none"><li>• Trabecular (tonographic) outflow facility</li><li>• IOP</li><li>• EVP</li></ul>
<p><b>Safety Assessments:</b> The assessment of safety and tolerability is a secondary objective of this study. The assessment of safety will be evaluated by:</p> <ul style="list-style-type: none"><li>• Ocular signs and symptoms / adverse events (AEs)</li><li>• Visual Acuity</li><li>• Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber.</li><li>• Ophthalmoscopy</li><li>• Pachymetry and Gonioscopy (screening only)</li><li>• Heart rate and blood pressure</li></ul>

## **Statistical Methods:**

### **Sample Size Determination**

Among the aqueous humor dynamics (AHD) parameters, trabecular outflow facility is of key interest and therefore used for the overall sample size calculation. Assuming a one-sided  $\alpha = 0.05$ , a standard deviation for the difference between treatments in the diurnal mean change from baseline of 0.07 mmHg (calculated with a common standard deviation of 0.06  $\mu\text{L}/\text{min}/\text{mmHg}$  within each treatment and a correlation of 40% between eyes within the same subject), and a difference in mean change from baseline between treatments (active - placebo) in diurnal means of 0.08  $\mu\text{L}/\text{min}/\text{mmHg}$ , a sample size of 16 yields >95% power.

Assuming approximately 20% of the randomized subjects may be non-evaluable i.e. either non-responders (see modified intent-to-treat population below for the definition of responder) or discontinued prior to Day 8, the required number of subjects to be randomized will be 20 subjects.

### **Analysis Populations**

#### **Modified Intent-to-Treat**

The modified intent-to-treat (mITT) population will include all randomized subjects who meet the following criteria: 1) have received at least one dose of study medication, 2) have all baseline measurements and all post-baseline measurements for trabecular outflow facility, and 3) have mean diurnal IOP that is at least 2 mmHg lower than baseline mean diurnal IOP in the same eye treated with Netarsudil (responders).

These subjects will be analyzed in accordance with the treatment they actually received, even if that treatment is different from the planned treatment (i.e., in the event of a randomization or dispensing error, subjects in the mITT population will be analyzed as treated). The mITT population will serve as the primary analysis population for efficacy variables.

#### **Per Protocol**

The per protocol (PP) population is a subset of the mITT, which will include those subjects (and their visits) who do not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. These subjects will be analyzed in accordance with the treatment they actually received, even if that treatment is different from the planned treatment (i.e., in the event of a randomization or dispensing error, subjects in the PP population will be analyzed as treated). The analysis with PP population is secondary.

#### **Safety**

All subjects who receive at least one dose of study drug will be included in the safety population. These subjects will be analyzed in accordance with the treatment they actually received, even if that treatment is different from the planned treatment (i.e., in the event of a randomization or dispensing error, subjects in the safety population will be analyzed as treated). Safety will be analyzed using the safety population.

### **Analysis of Primary Endpoint**

The primary endpoint is the mean change from baseline in the mean diurnal trabecular outflow facility on Day 8. The null and alternative hypotheses, based on the primary variable are as follows:

H01: The difference between study eyes treated with Netarsudil Ophthalmic Solution 0.02% and study eyes treated with Placebo, in the mean change from baseline of mean diurnal trabecular outflow facility = 0 on Day 8.

H11: The difference between study eyes treated with Netarsudil Ophthalmic Solution 0.02% and study eyes treated with Placebo, in the mean change from baseline of mean diurnal trabecular outflow facility > 0 on Day 8.

The null hypothesis will be tested using a paired t-test with  $\alpha=0.05$ . One-sided p-values, two-sided 90% CIs, and two-sided 95% CIs will be presented.

### **Analysis of Secondary Efficacy Endpoints**

Secondary AHD measures: IOP and EVP will be analyzed similarly to the primary endpoint.

Similar to the primary efficacy analysis, mean differences in diurnal means of AHD measures and mean

differences at the individual time points will be tested with paired t-tests. One-sided p-values, two-sided 90% CIs, and two-sided 95% CIs will be presented. Means within each treatment comparing diurnal mean on Day 8 with baseline diurnal mean and comparing individual time points on Day 8 with the corresponding time points at baseline visit will also be tested using paired t-tests. The same inferential statistics will be presented for these. Mean percent change from baseline in diurnal means of AHD measures and mean percent change from baseline in AHD measures at individual timepoints will be tested using paired t-tests. The same inferential statistics as for the primary endpoint will be presented for these.

All AHD measures will be summarized by treatment and visit/time point using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

Safety:

The observed and change from baseline in visual acuity (VA; logMAR) will be summarized using continuous descriptive statistics by visit/time point for each treatment. The proportion of subjects with a worsening of  $\geq 3$  lines ( $\geq 0.3$  logMAR) from baseline will also be summarized.

Shift tables for the slit-lamp biomicroscopy parameters will be provided, comparing follow-up visit with the baseline by treatment.

All treatment-emergent AEs (TEAEs, defined as an AE that occurs or worsens on or after the first treatment) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) to identify system organ class (SOC) and preferred term (PT).

An overall summary of TEAEs will be presented including the number of events and the number and percentage of subjects who experienced any TEAE, ocular TEAE, TEAE by maximum severity and relationship to study drug, death, treatment-emergent serious adverse event (SAE), and TEAEs resulting in withdrawal from study.

In addition, TEAEs will be summarized by SOC and PT for the following:

- TEAEs
- Ocular TEAEs
- Non-Ocular TEAEs
- Study Drug Related Ocular TEAEs
- Study Drug Related Non-Ocular TEAEs
- SAEs
- TEAEs by Severity

The above summaries will include the number and percentage of subjects experiencing at least one TEAE in each SOC and PT. The number and percentage of subjects experiencing any TEAE will also be provided. All percentages will use the number of safety subjects as the denominator. If a subject has more than one AE within SOC, the subject will be counted only once in that SOC. If a subject has more than one AE that codes to the same PT, the subject will be counted only once for that PT. The tabular summary will be sorted by descending order of frequency in SOC and PT in all subjects. Non-ocular AEs will be summarized at the subject level without assignment to a specific treatment. Ocular AEs will be summarized at the eye level by treatment group. Relationship to study drug will be rated by the Investigator as Not Related, Unlikely Related, Possibly Related, and Related. Related AEs will be classified as those rated as Possibly Related and Related. Severity will be rated by the Investigator as Mild, Moderate, and Severe. In the event that relationship or severity data are missing, the study analysis will follow the assumption of maximum relationship or severity in the summary tables.

All AEs will be presented in a by-subject data listing. In addition, SAEs, TEAEs leading to study withdrawal, and TEAEs leading to death will be listed separately.

**Date of Original Approved Protocol (Rev 0):**

10 May 2017

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**Prepared in:**

Microsoft Word 2010

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AHD	Aqueous humor dynamics
AM	Morning
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EVP	Episcleral Venous Pressure
GCP	Good Clinical Practice
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent To Treat
logMAR	Logarithm of Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
mITT	Modified Intent-to-Treat
mmHg	Millimeters Mercury
OD	Right Eye

OHT	Ocular Hypertension
OS	Left Eye
OTC	Over-the-Counter
POAG	Primary Open-Angle Glaucoma
PP	Per Protocol
PT	Preferred Term
QD	Once Daily
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TM	Trabecular Meshwork
US	United States
VA	Visual Acuity

## 1. INTRODUCTION

### 1.1 Background – Elevated IOP and Aqueous Humor Dynamics

Glaucoma is a progressive, neuropathology affecting approximately 60 million people globally, and uncontrolled, glaucoma can result in atrophy of the optic nerve, loss of visual fields and ultimately, irreversible blindness (Alward 1998, Casson 2012). Although any form of glaucoma can lead to vision loss, the most common form of the disease is primary open-angle glaucoma (POAG), which is defined by an open anterior chamber angle upon gonioscopic observation, some evidence of optic nerve damage or dysfunction (eg, visual field loss), and frequently, elevated intraocular pressure (IOP). A second disease condition, ocular hypertension (OHT), has been identified as one in which patients have an elevated IOP compared to population-based cut-off values, but with an apparent absence of optic nerve damage (Kass 2002). Elevated IOP is a major risk factor for development of glaucomatous visual field loss (The AGIS Investigators 2000), and a surrogate marker for disease progression, although other risk factors can also contribute to the development of glaucoma, including age, family history, and African race or Hispanic ethnicity (Varma 2004; Sommer 1991).

Pharmacological therapies aim to control and/or delay disease progression by reducing elevated IOP. However, given that every millimeter of IOP reduction is significant in delaying disease progression (Heijl 2011, Kass 2010 and Anderson 2003), and yet there is no single treatment that is universally effective, there is still a need for improved efficacy of glaucoma medications. The IOP itself is the result of the fluid dynamics of aqueous humor and its interaction with various tissues of the outflow system. IOP has a circadian variation as well as more rapid changes in response to multiple factors, including Valsalva maneuvers, changes in body position, water ingestion, and lid blinking.

IOP can be modeled as a function of 4 independent variables:

$$IOP = P_e + (Q - U) / c \quad (1)$$

where  $P_e$  is episcleral venous pressure (EVP),  $Q$  is the aqueous humor production rate,  $c$  is the trabecular outflow facility (inverse of outflow resistance), and  $U$  is the pressure-independent uveoscleral outflow rate. The interaction of the parameters that determine IOP is termed Aqueous Humor Dynamics (AHD).

In a glaucomatous eye, elevated IOP is due primarily to an abnormally high resistance to outflow through the trabecular meshwork (TM, [Stamer 2012]), the primary drainage pathway for aqueous humor produced by the ciliary body. Current treatments target reducing aqueous humor production, and/or shunting aqueous outflow to the uveoscleral pathway. In both cases, it is possible that the TM degradation continues unchecked, even if target IOP is reached and maintained. Thus a cause of elevated IOP – the diseased TM itself – is not addressed.

## 1.2 Investigational Product and Prior Experience

Netarsudil mesylate (AR-13324) is the active compound in netarsudil ophthalmic solution 0.02%. It is a novel Rho-kinase and norepinephrine transporter inhibitor developed by Aerie Pharmaceuticals, Inc. for reducing elevated IOP in patients with open-angle glaucoma (OAG) and/or ocular hypertension (OHT), and formulated to be dosed by topical instillation to the eye, 1 drop, once daily. Based on the results of non-clinical (Wang 2015, Kiel 2015) and early clinical (AR-13324-CS102) studies, netarsudil appears to have multiple mechanisms of action for lowering IOP, including increasing trabecular outflow facility and reducing EVP. Netarsudil has also been shown to decrease the production of aqueous humor in monkeys (Wang 2015), [REDACTED]

Aerie has completed a total of 8 clinical studies evaluating the dose response and dose frequency response of netarsudil ophthalmic solutions, as well as their ocular and systemic safety, including 3 well-controlled Phase 3 studies. In all Phase 3 studies, the efficacy of netarsudil ophthalmic solution 0.02% QD was non-inferior to timolol maleate ophthalmic solution 0.5% dosed twice daily (BID) in the Per Protocol (PP) and Intent To Treat (ITT) populations of subjects with maximum baseline IOP <25 mmHg, and <27 mmHg. Additionally, a favorable safety profile was demonstrated for netarsudil ophthalmic solution 0.02% QD through the duration of both studies. The majority of adverse events (AEs) were ocular and of mild or moderate intensity. [REDACTED]

A phase 1 study, AR-13324-CS102, evaluated the AHD of netarsudil in a population of healthy volunteers. The study demonstrated a mean reduction in IOP compared to baseline of 4.6 mmHg (~27%). Additionally, netarsudil demonstrated the following effects on AHD:

- Increase in outflow facility (~20% relative to baseline,  $p < 0.05$ )
- Decrease in EVP (~10% relative to baseline,  $p < 0.05$ )
- Decrease in aqueous flow (~15% relative to baseline,  $p < 0.08$ )
- Increase in uveoscleral outflow (calculated, not statistically significant relative to baseline)

The present study will evaluate the effect of netarsudil on AHD in subjects with POAG or OHT. Since trabecular outflow facility is of key clinical relevance and potentially a mechanism of action of netarsudil, this study will be powered with outflow facility as the primary efficacy parameter. IOP and EVP will also be evaluated.

## 1.3 Potential Risks to Human Subjects

Assessments, including measurement of IOP and outflow facility pose a minimal risk of corneal abrasion, similar to that of a routine eye exam. Phase 1 through Phase 3 safety data

indicate that there is minimal risk involved in a short (7 day) course of netarsudil, and treatment with placebo in one eye is of sufficiently short duration to not be considered a risk for disease progression. Please refer to the [Investigators' Brochure](#) for more detailed information on potential risks.

Previous animal ([AR-13324-APH07](#)) and human ([AR-13324-CS102](#), and [AR-13324-CS201](#)) studies indicate a minimal contralateral effect, thus suggesting that the paired-comparison design is appropriate.

## **2. STUDY OBJECTIVES**

### **2.1 Primary Objective(s)**

The primary objective of this study is to evaluate the effect on trabecular outflow facility of netarsudil ophthalmic solution 0.02%, compared to placebo, in subjects with POAG or OHT.

### **2.2 Secondary Objective(s)**

To evaluate the effect on IOP and EVP of netarsudil ophthalmic solution 0.02% compared to placebo in subjects with POAG or OHT.

To evaluate the ocular and systemic safety of netarsudil ophthalmic solution 0.02%.

### 3. INVESTIGATIONAL PLAN

#### 3.1 Overall Study Design and Plan

This will be a double-masked, placebo-controlled, paired-comparison study conducted at approximately 2 centers in the US to evaluate the effect of treatment with netarsudil ophthalmic solution 0.02% (netarsudil) on trabecular outflow facility. Netarsudil will be administered to one eye and Placebo to the contralateral eye once daily, 1 drop in the morning (QD, AM), in adult subjects at least 18 years of age with primary open angle glaucoma (POAG) or ocular hypertension (OHT). Study medication will be administered for 7 consecutive days, although the total time of subject participation in the study (including washout from prior treatment, if necessary) may be up to 7 weeks.

Subjects will be eligible to enroll in the study if they have a current diagnosis of POAG or OHT in both eyes (POAG in one eye and OHT in the contralateral eye is also acceptable), and may be treatment-naïve or taking topical ocular hypotensive medication. If necessary, subjects who agree to participate in the study will be required to washout from their current intraocular pressure (IOP)-lowering treatment for a minimum specified period of time (5 days to at least 4 weeks), according to the type of treatment. Subjects will attend a total of 3 study visits: a screening visit (Visit 1), to be conducted up to 6 weeks prior to a qualification visit (Visit 2, Day 1, baseline), and a final visit after 6 days on-treatment (Visit 3, Day 8, exit) where a member of the site staff will administer their 7<sup>th</sup> dose after completing their 08:00 hour assessments.

Both eyes must qualify for the study with an unmedicated (post-washout or treatment-naïve) IOP of >20 mmHg but <30 mmHg at 08:00 hours and >17 mmHg but <30 mmHg at 13:00 and 16:00 hours at the qualification visit. In order to be randomized into the study, eligible subjects must meet all of the inclusion, and none of the exclusion criteria at both the screening and at the qualification visit, following washout from their current ocular hypotensive treatment, if required.

If the subject continues to be eligible, they will be randomized at the end of their qualification visit (Visit 2, Day 1, baseline) to receive netarsudil ophthalmic solution 0.02% in one eye and Placebo in the contralateral eye for 7 days, QD (AM). Subjects will be asked to begin self-administration of their assigned medications in the morning on Day 2 following their baseline (Day 1) visit. Subjects will be instructed to administer 1 drop from each bottle of their study medication into the assigned eye for that bottle, every morning at approximately the same time (between 08:00 and 10:00 hours) for 6 consecutive days. On the day of the final (exit) visit (Visit 3, Day 8), subjects will return to the site at 08:00 hours for their final dose of study medication and to complete their on-treatment measurements before exiting.

Safety measures (including visual acuity, biomicroscopy, and AEs) will be evaluated at all visits. Efficacy assessments will include IOP at 08:00, 13:00 and 16:00 hours, and trabecular (tonographic) outflow facility and EVP, which will be measured at 13:00 and 16:00 hours. Tonographic outflow facility (primary endpoint) and IOP (secondary endpoint) will be

collected in all subjects. The other secondary endpoint, EVP, will be measured in a subset of subjects.

### **3.2 Rationale for Study Design and Control Group**

The primary treatment effect of netarsudil 0.02% is lowering IOP in subjects with glaucoma or OHT. From the results of mechanism of action studies conducted in both rabbits and monkeys, netarsudil is believed to lower IOP by several mechanisms including increasing aqueous humor outflow via the trabecular meshwork, reducing EVP and reducing aqueous humor production. Based on results from the Phase 1 study in healthy volunteers (AR-13324-CS102), the current study is designed to evaluate trabecular outflow facility, EVP and IOP in response to treatment with netarsudil ophthalmic solution 0.02% compared to placebo in subjects with elevated IOP.

The current design is powered on the most clinically-relevant component of AHD, trabecular outflow facility, thought to be the primary mechanism of action of netarsudil in lowering IOP.

Since the study treatment period is short (7 days), there is not believed to be a significant risk to subjects of the paired comparison design (i.e. active treatment in one eye and placebo in the fellow eye). Additionally, washing-out from their prior ocular hypotensive therapy, if necessary, should not pose a significant risk of clinically-relevant disease progression, since subjects will only be on investigational treatment or placebo for 7 days then can revert to their prior IOP-lowering treatment.

### **3.3 Study Duration and Dates**

The duration of treatment in this study is 7 consecutive days following randomization. Subjects will begin dosing on Day 2, in the morning following their Day 1 (qualification/baseline) visit, and dose for the next 6 days, returning to the site on Day 8 where their 7<sup>th</sup> and final dose will be administered. Subjects that are taking ocular hypotensive treatments at Screening will be required to wash-out of their current treatments as specified in [Table 1](#).

## 4. STUDY POPULATION SELECTION

### 4.1 Study Population

Adult subjects aged 18 years and older are eligible to be enrolled into this study. Subjects should have a current diagnosis of POAG or OHT. POAG in one eye and OHT in the other is acceptable. Subjects may be treatment-naïve or taking prescribed ocular hypotensive therapy at the time of screening. However if currently on ocular hypotensive treatment, they must discontinue from it for the duration of the study, and follow a prescribed washout period depending on the class of medication they are taking (see [Table 1](#)). Further details regarding subject eligibility are provided below (Sections 4.2 and 4.3).

Approximately 2 sites in the USA will participate in the study.

### 4.2 Inclusion Criteria

Subjects have to meet all of the following criteria at screening and qualification visits to enter into the study:

1. Must be 18 years of age or older
2. Diagnosis of POAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye is acceptable)
3. Unmedicated (post-washout, or treatment-naïve) IOP >20 mmHg and <30 mmHg in both eyes at 08:00 hours, and >17 mmHg but <30 mmHg at 13:00 and 16:00 hours at the qualification (Day 1, baseline) visit
4. Corrected visual acuity in each eye +1.0 on the logMAR scale or better by ETDRS chart or its equivalent in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye)
5. Be able and willing to provide signed informed consent and follow study instructions

### 4.3 Exclusion Criteria

Subjects meeting any of the following criteria during screening or qualification evaluations (eg, at the time of randomization) will be excluded from entry into the study:

#### Ophthalmic:

1. Clinically significant ocular disease (eg, corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications for one month is not judged to be safe by the Investigator

2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (as assessed by the Investigator, e.g. Grade 2 or less, Shaffer Scale). Note: Previous laser peripheral iridotomy is NOT acceptable
3. Intraocular pressure  $\geq 30$  mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification)
4. A difference in IOP between eyes  $>4$  mmHg (unmedicated) at any baseline time point
5. Use of more than two ocular hypotensive medications within 30 days of screening. Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as two medications
6. Known hypersensitivity to any component of the formulation (eg, benzalkonium chloride, etc.), or to topical anesthetic.
7. Previous glaucoma intraocular surgery or glaucoma laser procedures in either eye
8. Keratorefractive surgery in either eye (eg, radial keratotomy, PRK, LASIK, corneal cross-linking, etc.)
9. Report of ocular trauma in either eye within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the three months prior to screening
10. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or zoster keratitis in either eye at screening.
11. Use of ocular medication in either eye of any kind within 30 days of screening, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after screening), or c) lubricating drops for dry eye (which may be used throughout the study)
12. Mean central corneal thickness greater than 620  $\mu\text{m}$  in either eye at screening
13. Any abnormality preventing reliable applanation tonometry of either eye (eg, keratoconus, etc.)
14. Lack of suitable episcleral vein prior to performing EVP measurements at Visit 2/Day 1 (applicable to 1 site only [Mayo Clinic])

Systemic:

15. Clinically significant abnormalities (as determined by the Investigator) in any recent (within 6 weeks prior to screening) laboratory tests at screening which may affect the study results. Laboratory assessments, other than pregnancy tests in females of child-bearing potential and vital signs, will not be conducted for this study

16. Clinically significant systemic disease (eg, uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study
17. Participation in any investigational (interventional) study within 60 days prior to screening
18. Changes of systemic medication that could have an effect on IOP within 30 days prior to screening, or anticipated during the study, including use of any steroid-containing drug regardless of route of systemic administration (eg, steroid inhalers)
19. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative pregnancy test result at the screening examination and must not intend to become pregnant during the study

## **5. STUDY TREATMENTS**

### **5.1 Description of Treatments**

#### **5.1.1 Investigational Product**

Netarsudil ophthalmic solution 0.02% is a sterile, isotonic, buffered aqueous solution containing netarsudil mesylate (0.02%), boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.015%). The product formulation is adjusted to approximately pH 5.

#### **5.1.2 Placebo**

Netarsudil ophthalmic solution 0.02% placebo is a sterile, isotonic, buffered aqueous solution containing boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.015%). The product formulation is adjusted to approximately pH 5.

#### **5.1.3 Treatments of Subjects**

Enrolled subjects will receive both investigational products (IPs), Netarsudil Ophthalmic Solution 0.02% (QD AM) and Netarsudil Ophthalmic Solution Placebo (QD AM). Individual eyes will be randomized to receive active treatment or placebo; one treatment will be dosed in the right eye (OD), and the other treatment will be dosed in the left eye (OS). Each IP dose will be self-administered by the study subjects. For subjects deemed unable to self-administer the doses at the qualification visit (Visit 2, Day1), a guardian or caregiver will be asked to administer the medication.

### **5.2 Selection and Timing of Dose for Each Patient**

Masked kits containing identical bottles of IP labelled “right eye” or “left eye” will be provided to all subjects at the end of Visit 2 (Day 1, qualification, baseline). They will be instructed to begin self-administration in the morning of Day 2 at approximately the same time each day (between 08:00 and 10:00 hours) for the following 6 days, returning to the site on Day 8 where study personnel will administer the final dose.

### **5.3 Method of Assigning Patients to Treatment Groups**

A randomization schedule will be prepared by an independent individual (unmasked personnel) who is not involved in the day-to-day conduct of the study. Randomization will be stratified by site using permuted blocks, such that there will be an approximately equal number of subjects assigned to each of the two sequences ([Active Left Eye and Placebo Right Eye] and [Active Right Eye and Placebo Left Eye]) at each site.

The randomization schedule will be provided to the investigational site. The eligible subjects will be assigned a randomization number at the end of Visit 2, Day 1. Randomization numbers will be assigned sequentially to subjects in the order in which they become eligible

for randomization. The site staff will dispense to the subject the study kit labeled with the corresponding randomization number. Each subject kit will contain one bottle of each product labeled “RIGHT EYE” (OD) and “LEFT EYE” (OS). The randomization number will be recorded on the subject’s source document and electronic case report form (eCRF).

#### **5.4 Masking**

The study is designed as double-masked for the duration of the study. Assignment to treatment with netarsudil ophthalmic solution 0.02% or placebo will be randomized. The container-closure systems for both treatments are identical to preserve masking.

Given the nature of this study design, each subject will receive 2 bottles of masked medication, one labelled “right eye” and one labelled “left eye”. The final (7<sup>th</sup>) dose will be administered at the clinical site by study personnel, after all of the 08:00 hour procedures and measurements have been performed.

#### **5.5 Concomitant Therapy**

Intermittent use of over-the-counter (OTC) artificial tear lubricant products is acceptable, with a minimum of 10 minutes between OTC products and study medication. However, concurrent therapy with any form of ocular hypotensive medications (prescription or OTC) is not allowed during the study. Disallowed ocular medications include:

- Miotics,
- Epinephrine-related compounds,
- Carbonic anhydrase inhibitors (ocular or systemic),
- $\beta$ -adrenoceptor agonists,
- $\alpha$ - adrenoceptor antagonists, and
- Prostaglandin analogues

Systemic therapy with agents that could have a substantial effect on IOP within the 30 days prior to screening and throughout the study is an exclusion criterion; see [Table 1](#). Subjects who are stable on a  $\beta$ -adrenoreceptor antagonist (“ $\beta$ -blocker”) for cardiac arrhythmia, hypertension, etc. may enter the study provided their dose or dosing regimen has not been changed within the 3 months prior to Screening.

Contact lens wear must be stopped at least one week prior to the study, and during the study.

## 5.6 Restrictions

### 5.6.1 Prior Therapy

Subjects currently using ocular hypotensive medications must undergo a specific washout period as specified in Table 1. If the washout needs to be extended beyond 6 weeks (42 days) for logistical or other reasons, the Sponsor should be contacted.

**Table 1 Ocular Hypotensive Medication Washout Period**

Medication Class	Minimum Washout Period
Prostaglandins	4 weeks
$\beta$ -adrenoceptor antagonists	4 weeks
Adrenergic agonists (including $\alpha$ -agonists, such as brimonidine and apraclonidine)	2 weeks
Muscarinic agonists (e.g. pilocarpine), carbonic anhydrase inhibitors (CAIs, topical or oral)	5 days

[Hughes 2005](#)

### 5.6.2 Fluid and Food Intake

Not applicable

### 5.6.3 Subject Activity Restrictions

Not applicable

## 5.7 Treatment Compliance

All subjects will be instructed on the importance of following the daily dosing regimen.

[REDACTED] Subjects should be reminded to dose every morning, except on Day 8, the day of their final (exit) visit, when study personnel will administer the final dose at the clinical site, after all 08:00 hour measurements have been taken. All used and unused medication will then be collected by the appropriate site personnel. Patients may optionally use a Dosing Reminder worksheet that will be provided.

## 5.8 Packaging and Labeling

The container-closure systems for the investigational products are identical. The products for each individual treatment assignment will be packaged into identical subject kits; each subject kit will contain two bottles: one each of Netarsudil Ophthalmic Solution 0.02% and Netarsudil Ophthalmic Solution Placebo.

Each packaged unit will be labeled with an investigational label with the following minimal information: the study number, kit number, right/left eye designation, and storage statement, including a statement “Caution - New Drug - Limited by Federal (US) Law to Investigational Use” or equivalent.

## **5.9 Storage and Accountability**

The products should be stored in refrigerated conditions (2°C to 8°C/ 36°F to 46°F). The subject should be instructed to continue storing the product in the refrigerator (2°C to 8°C/ 36°F to 46°F) even after the bottle has been opened. Do not freeze the product.

Prior to dispensing to the subject, all investigational material must be stored in a secure location at the recommended long-term storage condition (2°C to 8°C) with strictly limited access documented by signature of authorized persons who may dispense investigational materials.

## **5.10 Investigational Product Retention at Study Site**

### **5.10.1 Receipt and disposition of study medication**

Study medication (i.e., investigational product) will be shipped to the Investigator’s site from a central depot. The study personnel at the Investigator’s site will verify study medication shipment records by comparing the shipping documentation accompanying the study medication to the study medication actually received at the Investigator’s site. If a discrepancy is noted, the appropriate individual at the Sponsor or designee must be notified immediately. The responsible person (e.g., study coordinator) at the Investigator’s institution has to account for all used, partially used and unused bottles of investigational products. The investigational product(s) must not be used outside this protocol. A Drug Accountability Log will be kept.

### **5.10.2 Return of study medication**

When the study is completed or is terminated by the Sponsor, all study material including used and unused study medication kits will be returned to the Sponsor’s designee. All study medication accounting procedures must be completed before the study is considered to be concluded. The responsible person at the Investigator’s institution has to account for all used, partially used and unused bottles of investigational products. The CRA assigned to the Investigator’s institution will complete a study drug returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused study medication kits to the Sponsor’s designee.

## **6. STUDY PROCEDURES**

All study procedures should be completed as described in the protocol within the timings specified, unless otherwise noted.

### **6.1 Informed Consent**

Prior to any study procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. Subjects and/or legally authorized representative then will be required to sign and date the informed consent form (ICF).

The ICF must have received approval/favorable review by a properly constituted Institutional Review Board (IRB) prior to use. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject undergoes any study related examination or activity before the subject has given written informed consent. It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, and should be notified that discontinuation from the study will not impact on their subsequent care.

### **6.2 Medical History**

Demographic data and any ongoing medication use will be collected and recorded. Any medications the subject took but discontinued within the 30 days prior to screening also will be recorded. Significant medical history will be collected and any current underlying medical conditions, including those that began within the last 30 days and which may have resolved before screening, additionally must be recorded.

### **6.3 Vital Signs**

#### **6.3.1 Heart Rate**

Subject heart rate will be measured at screening, and at 08:00 hours ( $\pm 30$  minutes) during each subsequent study visit attended by the subject. Heart rate will be determined only once during each study visit by the method described in [Appendix 2](#).

### **6.3.2 Blood Pressure**

Blood pressure will be measured once for each subject after the subject heart rate has been determined, with the subject in a sitting position. A mechanical or digital sphygmomanometer may be used, but effort should be made to use the same instrument and the same arm of the subject for each reading. Blood pressure will be determined only once during each study visit by the method described in [Appendix 2](#).

## **6.4 Clinical Laboratory Tests**

### **6.4.1 Laboratory Parameters**

Pregnancy testing will be conducted at any time prior to randomization for females of child-bearing potential. A female of child-bearing potential is defined as an adult woman unless she is one year post-menopausal or three months post-surgical sterilization. Any female who is pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control will be excluded from the study. All females of childbearing potential must have a negative pregnancy test result at the screening examination or at any time after screening and prior to Visit 2 (qualification, Day 1, baseline) and must not intend to become pregnant during the study.

No other laboratory testing is planned for this study.

### **6.4.2 Sample Collection, Storage and Shipping**

Not applicable.

## **6.5 Dispensing Investigational Product**

Study staff responsible for dispensing IP will be listed on the Delegation of Responsibilities log. When a subject meets all criteria for selection and has completed all screening and qualification assessments, the subject will be randomly assigned masked treatment to one eye (left eye or right eye) and masked placebo assigned to the contralateral eye, according to the randomization schedule (Section [5.3](#)). IP will be then dispensed to randomized subjects at the end of Visit 2 (Day 1), and subjects will be instructed to begin dosing the following morning (Day 2). The responsible study staff will account for all used and unused IP kits and their contents by maintaining an IP accountability log.

## **6.6 Efficacy Assessments**

The primary and key secondary efficacy assessments for this study are AHD per treatment. Mean change from baseline diurnal trabecular outflow facility (average of 13:00 and 16:00 hour measurements) per treatment on Day 8 is the primary efficacy endpoint. Baseline mean diurnal outflow facility is defined as the average of 13:00 and 16:00 hour measurements on Day 1, Visit 2. Secondary efficacy endpoints include:

- Mean change from baseline in mean diurnal IOP (average of 13:00 and 16:00 hour measurements) and mean diurnal EVP per treatment on Day 8
- Mean diurnal values for all AHD (trabecular outflow facility, IOP, EVP) per treatment on Day 8
- Mean values for all AHD at the individual 13:00 and 16:00 hour time points per treatment on Day 8
- Mean change from baseline for all AHD at the individual 13:00 and 16:00 hour time points per treatment on Day 8. Baseline individual time points are defined as the corresponding measurements on Day 1, Visit 2.
- Percent (%) change from baseline for all AHD per treatment on Day 8

## **6.7 Safety Assessments**

The assessment of safety and tolerability is a secondary objective of this study. The assessment of safety will be evaluated by:

- Ocular signs and symptoms / AEs
- Best Corrected Visual Acuity
- Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva and anterior chamber
- Ophthalmoscopy
- Pachymetry and Gonioscopy (screening only)
- Heart rate and blood pressure

## **6.8 Adverse Events Assessments**

If an AE/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. If a non-serious AE/adverse reaction is unresolved at the time of the last visit, efforts will be made to follow up until the AE/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

### **6.8.1 Performing Adverse Event Assessments**

The Principal Investigator at each site is responsible for defining and reporting any AE, its severity, seriousness, relatedness and outcome, and for ensuring proper and timely reporting of any events as described below. All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF.

## 6.8.2 Timing

Adverse events that occur at any time after the subject has signed informed consent, including during the washout period for prior ocular hypotensive medication for a particular subject, if necessary, (i.e. between Visit 1 and Visit 2) will be collected at the next visit (Visit 2) or earlier (i.e. during an unscheduled visit), and should be documented as part of the medical history.

Adverse events will be considered treatment-emergent (TEAEs) if they occur at any time from the time the subject receives the first dose of IP (Day 2, morning following Visit 2, baseline/qualification) until the subject's participation in the study has been completed. If a subject has an ongoing TEAE at the time of study completion, the ongoing TEAE must be followed-up and provided appropriate medical care until the event has resolved or stabilized.

## 6.8.3 Severity

Severity (intensity) of a TEAE is defined as a qualitative assessment of the level of discomfort of a TEAE, as determined by the Investigator or reported to him/her by the subject. The assessment of intensity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

**1 = Mild:** present, but not distressing, and no disruption of normal daily activity

**2 = Moderate:** discomfort sufficient to reduce or affect normal daily activity

**3 = Severe:** incapacitating, with inability to work or perform normal daily activity

A change in severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe, or from severe to moderate. In either case, the start and stop dates should be recorded.

Please note: a severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations. See Section 6.8.9 for reporting requirements of serious AEs (SAEs).

## 6.8.4 Relationship

The study medication relationship for each AE/adverse reaction should be determined by the Investigator using these explanations:

### **Not Related:**

The event is clearly related to other factor 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, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

**6.8.5 Action Taken with Study Drug**

The following actions may be taken with the study drug in response to an AE based on the clinical judgement of the Investigator, and should be recorded in the appropriate CRF:

- None
- Investigational Product Discontinued
- Investigational Product Interrupted
- Other Action Taken:
  - None
  - Non - Drug Therapy
  - New OTC or Rx Drug Added
  - Hospitalized less than 24 hours
  - Hospitalized greater than or equal to 24 hours
  - Unknown

Outcome of an AE is coded as follows, and may require completion of additional CRFs:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown/lost to follow-up

#### **6.8.6 Expectedness**

In previous clinical studies of netarsudil, the most frequently reported AE was conjunctival hyperemia. In the present study, investigators are asked to use the appropriate verbatim term on the AE form to describe this observation if it is increased from baseline:

- Redness related to instillation = “conjunctival hyperemia upon instillation”
- Redness that persists and is deemed not related to instillation = “conjunctival hyperemia”

In this regard, investigators are asked to appropriately note all observations of conjunctival hyperemia also on the biomicroscopy case report form. Please refer to the Investigator’s Brochure for further details on AEs observed in previous studies with netarsudil.

#### **6.8.7 Clinical Significance**

Determination of the significance of any AE for a particular subject, and in the context of the entire study, is the responsibility of the Investigator. The Sponsor additionally has overall responsibility for the safety of all subjects, and timely documentation and reporting of any safety concerns.

#### **6.8.8 Clinical Laboratory Adverse Events**

Other than pregnancy testing for females of child-bearing potential and vital signs, clinical laboratory testing is not planned for this study.

#### **6.8.9 Serious Adverse Events or Serious Suspected Adverse Events**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### 6.8.9.1 Definition

A "suspected adverse reaction" (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. For purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction", which means any AE caused by a drug.

A serious adverse event (SAE) or serious suspected adverse reaction (SSAR) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### 6.8.9.2 Reporting Serious Adverse Events or Serious Suspected Adverse Reactions

An investigator must immediately report to the Sponsor or Sponsor representative any SAE or SSAR (see Section 6.8.9.1 for definitions), whether or not considered drug-related, including those listed in the protocol or Investigator's Brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. The Investigator must report any SAE or SSAR that occurs during the course of the study and within four (4) weeks of last administration of the study medication. Study endpoints that are serious adverse events (eg, all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (eg, death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor. The investigator must record non-serious adverse events and report them to the Sponsor according to the timetable for reporting specified in the protocol. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or adverse events that are serious, unexpected (ie, not in the Investigator's Brochure) and judged related to the IP (a Serious Unexpected Suspected Adverse Reaction [SUSAR]), the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE. SAEs must be reported to the IRB according to the IRB requirements.

**Important:** The Investigator must report an SAE or SSAR occurring at his/her site to the Sponsor and IRB, regardless of causality.

Safety Email: [REDACTED]

Safety Fax: [REDACTED]

Aerie Pharmaceuticals, Inc. Medical Monitor contact information provided in Section 10.1.

Reports will be evaluated by the Medical Monitor. The IRB and Investigators at other study sites will be informed as required.

## 6.9 Concomitant Medication Assessments

Use of any medication – prescription or OTC should be recorded at the screening visit, and captured on the appropriate CRF, and the indication noted as part of the medical history. Treatments that are permitted to continue throughout the duration of the study will be recorded as concomitant medications at all subsequent visits.

Use of all medications should be documented on the appropriate CRF. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Investigator.

All medications which the subject has taken within 30 days prior to screening and during the study will be recorded in the CRF. The name of the drug, dose, route of administration, duration of treatment and indication will be recorded for each medication. For combination products (e.g., Contac®), the brand name is required. For non-combination products, the generic name is desired. The use of routine ophthalmic diagnostic pharmaceutical agents (e.g., local anesthetic) will be allowed, and individual documentation not required. Any change in dosing parameters should also be recorded in the CRF.

## 6.10 Removal of Subjects from the Study or Investigational Product

Subjects may be discontinued from the study at any time for any reason. Participation is entirely voluntary, and only possible if the subject has signed informed consent. Consent may be withdrawn at any time.

Enrollment of approximately 20 subjects for the study is allowed to account for a non-completion or disqualification rate of approximately 10%. Should more than 2 subjects discontinue, additional subjects may be enrolled after authorization by Aerie. Enrollment for this study will be competitive.

### **6.10.1 Completed Subject**

A completed subject is defined as one who completes all days of planned participation through completion of the Day 8 procedures.

### **6.10.2 Non-completing Subject**

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator and/or the Sponsor Safety Officer. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. In the event that discontinuation of treatment is necessary, the Investigator will make every attempt to complete all subsequent safety assessments.

### **6.10.3 Subject Discontinuation**

The subject may discontinue from the study for the following reasons (to be recorded on the CRF):

- Adverse Events (AEs including, in the opinion of the investigator, clinically relevant abnormalities and intercurrent diseases reported by the subject or observed by the investigator with documentation on the CRF).
- Administrative: This category is for reasons unrelated to the investigational product including:
  - Non-compliance (e.g., use of prohibited concomitant medication and/or failure to attend scheduled follow-up visits)
  - Other

All subjects who discontinue Investigational Product due to a report of an AE must be followed-up and provided appropriate medical care until their signs and symptoms have remitted or stabilized or until abnormal laboratory findings have returned to acceptable or pre-study limits.

### **6.10.4 Entire Study Terminated**

The entire study may be discontinued by the Investigator or the Sponsor. Prompt, written notice of reasonable cause to the other party (Sponsor or Investigator, respectively) is required. Prompt notice to the IRB and to regulatory authorities is also required.

### **6.10.5 Completed Study**

The study is completed when the planned enrollment has been completed, and all the enrolled subjects have completed the study.

## **6.11 Appropriateness of Measurements**

The ophthalmic and systemic measures used in this study are consistent with standard of care.

## 7. STUDY ACTIVITIES

A detailed Schedule of Visits and Procedures is provided in [Appendix 1](#). Details of procedures to be performed are provided in [Appendix 2](#).

### 7.1 Screening Visit (Visit 1)

This visit may take place at any time of the day.

Subjects with a diagnosis of POAG or OHT in both eyes (POAG in one eye and OHT in the fellow eye is acceptable) are eligible to be screened for this study. Individuals who are potential subjects will arrive at the Investigator's office. A member of the Investigator's staff will interview the individual as to their qualifications for participation in the study. Individuals will be asked to review the informed consent, discuss issues as needed, and to sign the form. A medical and ophthalmic history including systemic and ocular medication use will be taken, and demographic measures recorded. An examination will be conducted, including measurement of heart rate and blood pressure, and an ophthalmic examination (to include ocular symptoms, visual acuity (VA), central corneal thickness by ultrasound pachymetry, IOP, biomicroscopy, gonioscopy, and identification of episcleral vein (utilizing a slit lamp) that will be used for EVP measurement [REDACTED]). If no exclusion criteria are identified, dilated ophthalmoscopy will be performed. Subject symptoms will be queried. The investigator will evaluate the results of these examinations for possible enrollment of the individual into the study.

Subjects may be treatment-naïve or taking a prescribed IOP-lowering medication at the time of Screening. If the subject is currently taking an ocular hypotensive medication, once they have agreed to participate in the study and have signed informed consent, they will agree to washout from their current medication and refrain from taking it until they have exited the study. Washout from current ocular hypotensive medication will be conducted according to the times noted in [Table 1](#), and depends on the type of IOP-lowering treatment.

Evaluation of eyedrop instillation performance: Subjects will be provided a bottle of commercially available, multi-dose, non-medicated artificial tears in a room with access to water and soap. They will be asked to instill a drop of the artificial tear in each eye under the observation of a member of the investigator's staff. The staff will observe the subject to assure that the subject instills one drop (and one drop only) of the artificial tear into each eye, without touching the tip of the bottle to their eye or face ([Stone 2009](#)). The staff member may work with the individual to improve their delivery technique to meet this standard. If the subject cannot demonstrate proper delivery of the eye drop, or if staff member feels that the individual will be unable to do so consistently, then the subject will be excluded from further study participation.

All females of childbearing potential must have a negative pregnancy test result at the screening examination and must not intend to become pregnant during the study.

## 7.2 Treatment Period

### 7.2.1 Visit 2 (Day 1, Qualification/Baseline) Procedures

This visit should occur no more than 2 to 7 days following the Screening visit, if the subject is treatment-naïve, or following the appropriate washout time prescribed for the IOP-lowering medication(s) they were taking at screening ([Table 1](#)).

Individuals who do NOT meet the IOP requirements at any of the timepoints in this visit may return for up to 2 additional visits within 1 week of failing this visit. Individuals returning for an unscheduled visit within 1 week to re-attempt IOP qualification are required to ONLY re-measure IOP in both eyes.

Upon return of the requalification visit, such individuals' IOP measurements would need to qualify at all timepoints (08:00, 13:00, and 16:00)

Individuals who screen fail due to IOP being  $\geq 30$  mmHg in either eye (exclusion criterion) MAY NOT return for additional qualification visits.

#### 7.2.1.1 Visit 2 08:00 hours ( $\pm 30$ min)

Vital signs will be collected (heart rate and blood pressure), and the subject's general well-being and ocular symptoms will be collected (including medical history, concomitant medications and any adverse events). An ocular examination will then take place, including VA, IOP, and biomicroscopy.

Please note that the episcleral vein may be assessed during this visit timepoint if it was not able to be assessed during the Screening visit.

IOP should be  $>20$  mmHg and  $<30$  mmHg in both eyes in order for the subject to continue to be eligible for qualification and enrollment into the study. Furthermore, the IOP should not differ by more than 4 mmHg between the eyes. Subjects will be re-examined at 13:00 hours. Note; subjects are free to leave the site between visits, provided they agree to not participate in strenuous activities or consume alcohol, and return promptly for the next visit.

#### 7.2.1.2 Visit 2 13:00 hours ( $\pm 30$ min)

The following procedures will be conducted:

- IOP, which must be  $>17$  mmHg but  $<30$  mmHg in order for the subject to be considered eligible to proceed with the Qualification visit.
- EVP (see [Appendix 2](#) for procedures).
- Trabecular (tonographic) outflow facility (see [Appendix 2](#) for procedures).

The subject will then return for their final Qualification examination at 16:00 hours. Note; subjects are free to leave the site between visits, provided they agree to not participate in strenuous activities or consume alcohol, and return promptly for the next visit

#### 7.2.1.3 Visit 2 16:00 hours ( $\pm$ 30 min)

The following procedures will be conducted:

- IOP, which must be  $>17$  mmHg but  $<30$  mmHg in order for the subject to be considered eligible to proceed in the study.
- EVP (see [Appendix 2](#) for procedures)
- Trabecular (tonographic) outflow facility (see [Appendix 2](#) for procedures)

Provided the Investigator is satisfied that the subject meets all of the Inclusion criteria and none of the Exclusion criteria, and the subject continues to be willing to participate in the study, then the subject will be enrolled and randomized to a treatment schedule. After obtaining randomization information, the appropriate subject kit will be provided to the subject.

The subject will be instructed to begin dosing the following day (Day 2) between 08:00 and 10:00 hours, and to dose every day for 6 days at the same time (between 08:00 and 10:00 hours). One drop from the bottle labelled “Right Eye” should be dispensed into the right eye every day, and one drop from the bottle labelled “Left Eye” into the fellow eye once every day. Subjects will return to the site 7 days later (Day 8) BEFORE taking their study medication for their exit visit procedures.

#### 7.2.2 Visit 3 (Day 8, Exit)

This visit should occur 7 days after Visit 2 (qualification/baseline visit), and the subject should be instructed to bring all medications with them to the site. The subject should not take their study medication before arriving at the site, but should be instructed that they will administer their medication at the site following their 08:00 hour assessments have been performed.

##### 7.2.2.1 Visit 3 08:00 hour ( $\pm$ 30 min)

Subjects will be asked how they have been feeling since their last visit, and to describe any TEAEs they may have experienced.

The following procedures will be performed:

- Heart rate and blood pressure
- Ocular symptoms
- Visual Acuity

- Biomicroscopy
- IOP

Site personnel will then instill their final doses of study medication and all medication, used and unused, will be collected from the subject. The subject will then be asked to return for their next assessments at 13:00 hours. Note; subjects are free to leave the site between visits, provided they agree to not participate in strenuous activities or consume alcohol, and return promptly for the next visit.

#### 7.2.2.2 Visit 3 13:00 hours ( $\pm$ 30 min)

The following procedures will be conducted:

- IOP
- EVP (see [Appendix 2](#) for procedures).
- Trabecular (tonographic) outflow facility (see [Appendix 2](#) for procedures).

The subject will then return for their final examination at 16:00 hours. Note; subjects are free to leave the site between visits, provided they agree to not participate in strenuous activities or consume alcohol, and return promptly for the next visit

#### 7.2.2.3 Visit 3 16:00 hours ( $\pm$ 30 min)

The following procedures will be conducted:

- IOP
- EVP (see [Appendix 2](#) for procedures).
- Trabecular (tonographic) outflow facility (see [Appendix 2](#) for procedures).

The subject will then be thanked for their participation in the study, and will be dismissed.

### 7.3 **Unscheduled Visit**

An unscheduled visit is any visit to the Investigator other than the specific visits requested in the protocol, as may be possibly required for the subject's ophthalmic condition. The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any TEAEs in the eCRF. If the unscheduled visit occurs prior to Day 8, and the subject is to discontinue from the study for any reason, every effort should be made by the site to conduct the assessments and procedures outlined above ([Section 7.2.1.3](#)) for the Exit visit.

## **8. QUALITY CONTROL AND ASSURANCE**

The progress of the 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 consent forms
- Records of study medication receipt, storage, preparation, and disposition
- Regulatory files related to this study

## **9. PLANNED STATISTICAL METHODS**

### **9.1 General Considerations**

All statistical analyses will be performed by the Sponsor designee using SAS® software. A separate Statistical Analysis Plan will be produced that will provide complete details regarding the data handling and analysis methods.

Continuous summary statistics (sample size, mean, SD, median, minimum, and maximum) will be presented by treatment for each time point (and for the diurnal mean) at each visit and for the change from baseline and percent change from baseline. All study data will be listed by treatment, subject, and time point (as applicable).

For measurements of AHD, baseline will refer to the time-relevant measure at Visit 2, Day 1 (e.g., IOP at 13:00 hours at Visit 2 will be the baseline for IOP at 13:00 hours at Visit 3). For all other variables, baseline is defined as the last measurement prior to the first dose of study medication.

All statistical tests will use one-sided significance level of 5%. Where applicable, 2-sided 90% (equivalent to one-sided 90% confidence intervals [CIs]) and 95% CIs will be reported

### **9.2 Determination of Sample Size**

Among the AHD parameters, trabecular outflow facility is of key interest and therefore used for the overall sample size calculation. Assuming a one-sided  $\alpha = 0.05$ , a standard deviation for the difference between treatments in the mean change from baseline in diurnal means of 0.07 mmHg (calculated with a common standard deviation of 0.06  $\mu\text{L}/\text{min}/\text{mmHg}$  within each treatment and a correlation of 40% between eyes within the same subject), and a difference in mean change from baseline between treatments (active - placebo) in diurnal means of 0.08  $\mu\text{L}/\text{min}/\text{mmHg}$ , a sample size of 16 subjects (32 eyes) yields greater than 95% power.

Assuming approximately 20% of the randomized subjects will be non-evaluable i.e. either non-responders (see modified intent-to-treat population below for the definition of responder) or discontinue prior to Day 8, the required number of subjects to be randomized will be 20 subjects.

### **9.3 Analysis Populations**

#### **9.3.1 Modified Intent-to-Treat (mITT) Population**

The modified intent-to-treat (mITT) population will include all randomized subjects who meet the following criteria: 1) have received at least one dose of study medication, 2) have all baseline measurements and all post-baseline measurements for trabecular outflow facility, and 3) have mean diurnal IOP that is at least 2 mmHg lower than baseline mean diurnal IOP in the same eye treated with Netarsudil (responders).

These subjects will be analyzed in accordance with the treatment they actually received, even if that treatment is different from the planned treatment (i.e., in the event of a randomization or dispensing error, subjects in the mITT population will be analyzed as treated). The mITT population will serve as the primary analysis population for efficacy variables.

### **9.3.2 Per Protocol (PP) Population**

The per protocol (PP) population is a subset of the mITT, which will include those subjects who do not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. These subjects will be analyzed in accordance with the treatment they actually received, even if that treatment is different from the planned treatment. The analysis with PP population is secondary.

### **9.3.3 Safety Population**

All subjects who receive at least one dose of study drug will be included in the safety population. These subjects will be analyzed in accordance with the treatment they actually received, even if that treatment is different from the planned treatment (i.e., in the event of a randomization or dispensing error, subjects in the safety population will be analyzed as treated). Safety will be analyzed using the safety population.

## **9.4 Statistical Methods**

### **9.4.1 Demographics and Baseline Characteristics**

Demographic and baseline characteristics will be summarized using descriptive statistics and presented in individual listings.

### **9.4.2 Subject Disposition**

Subject enrollment, inclusion into each analysis population, and withdrawal from the study will be summarized and listed.

### **9.4.3 Efficacy Analysis**

The primary endpoint is the mean change from baseline in the mean diurnal trabecular outflow facility on Day 8. The null and alternative hypotheses, based on the primary variable are as follows:

H01: The difference between study eyes treated with Netarsudil Ophthalmic Solution 0.02% and study eyes treated with Placebo, in the mean change from baseline of mean diurnal trabecular outflow facility = 0 on Day 8.

H11: The difference between study eyes treated with Netarsudil Ophthalmic Solution 0.02% and study eyes treated with Placebo, in the mean change from baseline of mean diurnal trabecular outflow facility > 0 on Day 8.

The null hypothesis will be tested using a paired t-test with  $\alpha=0.05$ . One-sided p-values, two-sided 90% CIs, and two-sided 95% CIs will be presented.

Secondary AHD measures: IOP and EVP will be analyzed similarly to the primary endpoint.

Similar to the primary efficacy analysis, mean differences in diurnal means of AHD measures and mean differences at the individual time points will be tested with paired t-tests. One-sided p-values, two-sided 90% CIs, and two-sided 95% CIs will be presented. Means within each treatment comparing diurnal mean on Day 8 with baseline diurnal mean and comparing individual time points on Day 8 with the corresponding time points at baseline visit will also be tested using paired t-tests. The same inferential statistics will be presented for these.

Mean percent change from baseline in diurnal means of AHD measures and mean percent change from baseline in AHD measures at individual timepoints will be tested using paired t-tests. The same inferential statistics as for the primary endpoint will be presented for these.

All AHD measures will be summarized by treatment and visit/time point using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

#### **9.4.4 Safety Analysis**

The observed and change from baseline in BCVA (logMAR) will be summarized using continuous descriptive statistics by visit/time point for each treatment. The proportion of subjects with a worsening of  $\geq 3$  lines ( $\geq 0.3$  logMAR) from baseline will also be summarized.

Shift tables for the slit-lamp biomicroscopy parameters will be provided, comparing follow-up visit with the baseline by treatment.

All TEAEs (TEAEs, defined as an AE that occurs or worsens on, or after the first treatment) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) to identify system organ class (SOC) and preferred term (PT).

An overall summary of TEAEs will be presented including the number of events and the number and percentage of subjects who experienced any TEAE, ocular TEAE, TEAE by maximum severity and relationship to study drug, death, treatment-emergent SAE, and TEAEs resulting in withdrawal from study.

In addition, TEAEs will be summarized by SOC and PT for the following:

- TEAEs
- Ocular TEAEs
- Non-Ocular TEAEs
- Study Drug Related Ocular TEAEs

- Study Drug Related Non-Ocular TEAEs
- SAEs
- TEAEs by Severity

The above summaries will include the number and percentage of subjects experiencing at least one TEAE in each SOC and PT. The number and percentage of subjects experiencing any TEAE will also be provided. All percentages will use the number of safety subjects as the denominator. If a subject has more than one AE within SOC, the subject will be counted only once in that SOC. If a subject has more than one AE that codes to the same PT, the subject will be counted only once for that PT. The tabular summary will be sorted by descending order of frequency in SOC and PT in all subjects. Non-ocular AEs will be summarized at the subject level without assignment to a specific treatment. Ocular AEs will be summarized at the eye level by treatment group.

Relationship to study drug will be rated by the Investigator as Not Related, Unlikely Related, Possibly Related, and Related. Related AEs will be classified as those rated as Possibly Related and Related. Severity will be rated by the Investigator as Mild, Moderate, and Severe. In the event that relationship or severity data are missing, the study analysis will follow the assumption of maximum relationship or severity in the summary tables.

All AEs will be presented in a by-subject data listing. In addition, SAEs, TEAEs leading to study withdrawal, and TEAEs leading to death will be listed separately.

### **9.5 Missing or Inconclusive Data Handling**

Missing data will not be imputed. For measurements of AHD, if the result is missing in one eye, then the result for the contralateral eye will be assumed to be missing at the same time point.

### **9.6 Adjustments for Multiplicity**

No adjustments for multiplicity are planned.

### **9.7 Interim Analysis**

Not applicable.

## 10. ADMINISTRATIVE CONSIDERATIONS

### 10.1 Investigators and Study Administrative Structure

The principal investigator is responsible for all site medical-related decisions. The qualified sponsor medical monitor responsible for the safety conduct of this study:

[REDACTED]

[REDACTED]

### 10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This study is to be conducted in accordance with IRB regulations (ie, US 21CFR Part 56.103) and GCP. The Investigator must obtain appropriate approval from a properly constituted IRB prior to initiating the study and re-approval at least annually. A copy of the letter from the IRB indicating approval of an Investigator must be received by the Sponsor prior to conducting any study-specific procedures.

The protocol, protocol amendments, ICF, and all documents that will be provided to subjects (for example, subject diary, subject dosing instructions) will be submitted to the central and/or local IRB(s) for review and approval.

### 10.3 Ethical Conduct of the Study

The study will be conducted according to this clinical protocol and will be governed by the following directives and guidelines:

- US Code of Federal Regulations, Title 21
- ICH – Consolidated Good Clinical Practice Guideline (E6)
- Standard Operating Procedures (SOPs) of the Sponsor and any other vendors participating in the conduct of the study

### 10.4 Subject Information and Consent

Informed consent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

All ICFs must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the Sponsor prior to submission to the governing IRB and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study if directed by the IRB.

### **10.5 Subject Confidentiality**

The Investigator and his/her staff will maintain all personal subject data collected and processed for the purposes of this study using adequate precautions to ensure confidentiality, in accordance with local, state and federal laws and regulations.

Monitors, auditors and other authorized representatives of Aerie, the IRB approving this study, and government regulatory authorities (eg, FDA and other foreign regulatory agencies) may be granted direct access to the study subject's original medical and study records for verification of the data or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of this study's results may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but subject identities will not be disclosed in these documents.

### **10.6 Study Monitoring**

Clinical research associates hired or contracted by the Sponsor will be responsible for monitoring the study sites and study activities. They will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on subject enrollment and on study site performance. Among others, the following items will be reviewed:

- study progress
- compliance with the protocol
- completion of eCRFs
- dispensing, storage, and accountability of IP, including unmasking of IP
- source data verification
- AE and SAE reporting
- essential documents contained within the regulatory binder

For source data verification (i.e., comparison of eCRF entries with subject records), data will be 100% source verified and will include, but not be limited to: subject identification, informed consent and assent, if applicable (procedure, signature, and date), selection criteria, and primary efficacy and safety parameters (i.e., AEs).

## 10.7 Case Report Forms and Study Records

Study data will be recorded via eCRFs. Each authorized study staff member will receive a unique access account in order to use the Electronic Data Capture (EDC) system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to the eCRF via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

Source document information should be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

The study records must include a copy of each Investigator's CV and medical license, completed, FDA Form 1572 or statement of Investigator, each eCRF, subject charts/source documents, Investigator's Brochure, protocol, protocol amendments, correspondence with the Sponsor and the IRB, IP storage, receipts, returns and dispensing records, Delegation of Responsibilities Log, site training records, records of site monitoring, unmasking documentation, AE and SAE reporting, IRB approvals, advertisements, written information provided to subjects, and subject completed ICFs. If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (e.g., Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

## 10.8 Protocol Deviations

A protocol deviation occurs when there is non-adherence to study procedures or schedules which does not involve inclusion/exclusion criteria or the primary efficacy endpoint and which does not place the subject at any added risk or affect the data quality or study outcome. Examples of deviations include common out of window visits or timed procedures, a missed procedure, etc. Sites will record protocol deviations in the study records. To the extent possible, sites will make their best efforts to quickly remedy deviations.

The site will contact the Sponsor for clarification of inclusion/exclusion criteria as needed prior to enrollment of a study subject. The Sponsor will document clarification requests and responses. **No waivers to inclusion or exclusion criteria are allowed.** If a potential subject does not meet all inclusion and exclusion criteria during screening, that subject may not be enrolled in the study.

The site will notify the Sponsor or their representative and IRB within 3 days of becoming aware of any significant protocol deviation. Typically, significant protocol deviation include significant deviations from the inclusion and exclusion criteria that may impact interpretation or the quality of efficacy information or the safety of a subject, concomitant medication

restrictions, or any other protocol requirement that results in a significant added risk to the subject or has an impact on the quality of the data collected or the outcome of the study.

The Sponsor will review, designate, and/or approve all protocol deviations prior to database lock.

### **10.9 Access to Source Documentation**

Monitors, auditors, and other authorized representatives of the Sponsor, the governing IRB(s), the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

### **10.10 Data Generation and Analysis**

For data captured on a paper CRF (eg, subject diary, subject questionnaire), the completed CRF will be sent to the data management CRO after monitoring is complete or will be faxed to the data management CRO upon completion by the subject. Once the CRFs are monitored in the EDC system and double data entry of the paper CRFs into the clinical database has been completed, the data management CRO and the Sponsor will further check the CRFs for completeness and plausibility of the data. The data management CRO will use quality systems in order to verify accurate and complete data entry, including additional checks of the data once entered in a database (eg, range checks, cross checks and other edit checks). Where required, the Investigator will be asked for supplementary information through a query.

Data will be checked per CRO's SOPs. The database will be locked and a biostatistician will complete the analyses of the data in accordance with the Statistical Analysis Plan.

### **10.11 Retention of Data**

The Investigator shall retain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated, or for a period of 2 years after all investigations with the drug are discontinued and FDA has been duly notified in the circumstance that no application is to be filed or the application is not approved for such indication. The Sponsor will inform the Investigator when the study records can be destroyed.

### **10.12 Financial Disclosure**

The Principal Investigator and Sub-investigators (as listed on Form FDA 1572) will provide financial disclosure information prior to participation in the study. The Principal Investigator and any Sub-investigators will notify the Sponsor promptly of any required revision to their financial disclosure status during the term of this study, annually, or at the end of the study

(if applicable). The Principal Investigator and Sub-investigators will provide updated financial disclosure information upon the Sponsor's written request following completion of the study.

### **10.13 Publication and Disclosure Policy**

Sponsor policy encourages the presentation and publication of clinical study data. Prior to any presentation of results, draft versions of manuscripts will be made available to co-authors and to the Sponsor for review and comment. At least 30 days (for abstracts) or 60 days (for full papers) should be allowed for comments prior to submission of manuscripts or abstracts for consideration of acceptance of presentation or publication.

## 11. REFERENCES

### 11.1 External References

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## **11.2 Internal References**

1. Aerie Pharmaceuticals, Inc. Investigators' Brochure
2. Aerie Pharmaceuticals, Inc. AR-13324-CS102 Clinical Study Report
3. Aerie Pharmaceuticals, Inc. AR-13324-CS201 Clinical Study Report
4. Aerie Pharmaceuticals, Inc. AR-13324-APH07 Non-Clinical Study Report

### Appendix 1 Schedule of Events

Day (D)/Week(W)/Month(M)	Screening	Qualification/Day 1			Exit/Day 8		
Visit	1	2/Baseline <sup>7</sup>			3/On-drug <sup>7</sup>		
Hour	--	08:00	13:00	16:00	08:00	13:00	16:00
Informed Consent	X						
Inclusion/Exclusion	X	X	X	X			
Demography	X						
Medical/Ophthalmic History	X						
HR/BP	X	X			X		
Pregnancy test <sup>1</sup>	X						
Ocular symptoms/AEs <sup>2</sup>	X	X			X		
Visual Acuity (ETDRS)	X	X			X		
IOP	X	X	X	X	X	X	X
Biomicroscopy	X	X			X		
Gonioscopy <sup>3</sup>	X						
Pachymetry <sup>3</sup>	X						
Ophthalmoscopy (dilated)	X						
Eye-Drop Instillation Evaluation	X						
EVP <sup>4</sup>	X <sup>6</sup>		X	X		X	X
Tonography			X	X		X	X
Study meds dispensed				X			
Study meds instilled <sup>5</sup>					X		
Study meds collected					X		
Study completed							X

1. Pregnancy test for females of child-bearing potential only.
2. Ocular Symptoms: Patients will be queried at each visit “how are your eyes feeling” and TEAEs will be documented on the AE form. Additional symptoms reported after screening and before randomization will be documented on the medical history form.
3. Gonioscopy within 3 months prior to screening, and Pachymetry within 1 week of screening are acceptable.
4. Measurement of EVP will only be conducted at 1 site (██████████).
5. Study medications to be instilled after 08:00 hour measurements are completed on Day 8.
6. Only an assessment of a suitable episcleral vein prior to performing EVP measurements at Visit 2/Day 1. If unable to assess at screening, it may be assessed at Visit 2 during the 08:00 timepoint
7. A visit variation of ± 30 minutes is allowed.

[REDACTED]

**Table 2 Comparison of Snellen ratio and logMAR units**

<i>Snellen ratio</i>	<i>logMAR</i>
20/200	+1.0
20/160	+0.9
20/125	+0.8
20/100	+0.7
20/80	+0.6
20/62.5	+0.5
20/50	+0.4
20/40	+0.3
20/32	+0.2
20/25	+0.1
20/20	+0.0
20/16	-0.1
20/12.5	-0.2
20/10	-0.3

[REDACTED]

### **Appendix 3 Sponsor's Obligations**

Aerie Pharmaceuticals, Inc. is committed to:

1. Complying with the local health authority regulations for the conduct of clinical research studies.
2. Informing the Investigator of any new information about the investigational product that may affect the subject's welfare or may influence the subject's decision to continue participation in the study.
3. In the event of a serious adverse experience, whether related to the use of the study medication or not, or the death of a subject, the Sponsor is responsible for notifying the regulatory authority(ies) immediately (see Section 6.8.9, Adverse Event Assessments).
4. When the study is terminated the Sponsor should promptly inform the regulatory authority(ies) of the termination and the reason(s) for it. The IRB should also be informed promptly and provide the reason(s) for the termination by the Sponsor as specified by the applicable regulatory requirement(s).
5. Providing to the Investigator the most up-to-date editions of the Clinical Investigator's Brochure (for the investigational product), the protocol, Serious Adverse Experience forms, and a full set of Case Report Forms for each subject entered into the study to document the study evaluation parameters.
6. Providing study medications suitably masked/blinded, coded and packaged for use with subjects entered into the study.
7. Providing statistical and report writing resources to complete appropriate reporting of study results.
8. Ensuring equity considerations among all Investigators in multicenter studies, including all matters of publications and meeting presentations, etc. (where applicable).
9. Prepare an FDA Form No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) or Sponsor's equivalent

## **Appendix 4 Investigator's Obligations**

The Investigator is obligated to:

1. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Investigator is responsible for notifying the Sponsor Safety Officer immediately (see Section 6.8, Adverse events). The Investigator must also notify the Sponsor Representative and the Institutional Review Board (IRB) to which he/she is responsible.
2. Prior to initiating the study, sign and return to the Sponsor Representative, the relevant form (Statement of Investigator form provided by the Sponsor for studies involving non significant risk devices, or OTC drugs; or an FDA No. 1572 is required for IND Phase I, II, III and IV studies). Each sub-Investigator who will assist in the study is to be identified in the required form. The current curriculum vitae (signed and dated) of the principal Investigator and of each sub-Investigator named in the Statement of Investigator form or 1572 form is to accompany the form.
3. Cooperate with the Sponsor on the preparation of an FDA Form No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators).
4. Obtain and submit to the Sponsor a copy of his/her IRB approval of the protocol prior to initiating the study.
5. Obtain signed informed consent from each subject or his/her legal guardian prior to acceptance of the subject into the study.
6. Read, and agree to adhere to the study protocol prior to the initiation of the study. Deviations from the study protocol are not to be implemented without the prior written approval of the Sponsor and IRB, unless protection of the safety and welfare of study subjects requires prompt action. During the study, if the Investigator feels that in his/her clinical judgment, it is necessary to promptly terminate one or more subjects from the study, or to promptly implement reasonable alternatives to, or deviations from the protocol in consideration of the safety of study subjects, the Sponsor is to be notified of these terminations, alternatives, and deviations, and the reasons for such changes are to be documented in the study records. The Investigator is to also notify his/her IRB of any such changes.
7. Accurately record, at the Investigator's site, all required data on each subject's electronic Case Report Form.
8. Keep accurate records of the number of study medication or device units received from the Sponsor and dispensed or administered to each subject during the study, and return any unused study medication or devices to the Sponsor at the completion of the study.

Before returning the study medications or devices to the Sponsor, a detailed inventory should be recorded and placed in the Investigator's file.

9. Assure that Investigational Products will be dispensed or administered only to subjects under his/her personal supervision, or under the supervision of authorized sub-Investigators responsible to him/her.
10. Allow a representative of the Sponsor and/or representatives of health regulatory agencies to inspect all Case Report Forms and corresponding portions of each study subject's source documentation (ie, original office, hospital, and laboratory records) at mutually convenient times at regular intervals during the study, and upon request after the study has been completed. The purpose of these on site monitoring visits is to provide the Sponsor the opportunity to evaluate the progress of the study, document compliance with the protocol and with regulatory requirements, verify the accuracy and completeness of subject electronic Case Report Forms, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.
11. Provide the governing IRB with a brief (ie, one to three pages) Investigator's summary within 90 working days of the study completion.
12. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study.
13. Maintenance of records
  - a. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the Sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.
  - b. Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
  - c. Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

If for any reason the Investigator withdraws from the responsibility of maintaining the study records for the required period of time, custody of the records may be transferred to any other person who will accept responsibility for the records. The Sponsor is to be notified in writing of any such transfer.

## **Appendix 5 Declaration of Helsinki**

### Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

#### I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest with the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her

consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

## II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

13. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.
14. The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
15. In any medical study, all subjects - including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic methods.
16. The refusal of the subject to participate in a study must never interfere with the doctor subject relationship.
17. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.
18. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

### III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECT (NONCLINICAL BIOMEDICAL RESEARCH)

19. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.
20. The subjects should be volunteers - either healthy person or subjects for whom the experimental design is not related to the subject's illness.
21. The Investigator or the team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
22. In research on man, the interest of science and society should never take precedence over consideration related to the well-being of the subject.