AR-13324-CS205

A prospective, double-masked, randomized, multicenter, placebo-controlled, parallel-group study assessing the safety and ocular hypotensive efficacy and optimum concentration to be used clinically of netarsudil ophthalmic solution in Japanese/Japanese-American subjects with open-angle glaucoma or ocular hypertension in the United States

NCT03310580

17Jul2017

Clinical Study Protocol:

Study Title:	A prospective, double-masked, randomized, multicenter, placebo-controlled, parallel-group study assessing the safety and ocular hypotensive efficacy and optimum concentration to be used clinically of netarsudil ophthalmic solution in Japanese/Japanese-American subjects with open-angle glaucoma or ocular hypertension in the United States
Study Number:	AR-13324-CS205
Study Phase:	2
Product Name:	Netarsudil 0.02% and 0.04% Ophthalmic Solution
Indication:	Reduction of elevated intraocular pressure (IOP) in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)
Investigators:	Multicenter
Sponsor:	Aerie Pharmaceuticals, Inc.
Sponsor Contact:	135 US Highway 206, Suite 15 Bedminster, NJ 07921 (908) 470-4320
Medical Monitor:	[redacted]

	Date
Original Protocol (Rev 0):	17 July 2017

Confidentiality Statement

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A prospective, double-masked, randomized, multicenter, placebo-controlled, parallel-group study assessing the safety and ocular hypotensive efficacy and optimum concentration to be used clinically of netarsudil ophthalmic solution in Japanese/Japanese-American subjects with open-angle glaucoma or ocular hypertension in the United States

Study No: AR-13324-CS205
Original Protocol Date: 17 July 2017
Protocol Version No: Rev 0
Protocol Version Date: 17 July 2017

Role	Contact information
Clinical Operations	[redacted]
Aerie Management and Sponsor Safety Officer	[redacted]

Medical Monitor

Clinical Laboratory

Biostatistics and Data Management

SYNOPSIS

Sponsor:
Aerie Pharmaceuticals, Inc.

Name of Finished Product:
Netarsudil 0.02% and 0.04% Ophthalmic Solution

Name of Active Ingredients:
Netarsudil

Study Title:
A prospective, double-masked, randomized, multicenter, placebo-controlled, parallel-group study assessing the safety and ocular hypotensive efficacy and optimum concentration to be used clinically of netarsudil ophthalmic solution in Japanese/Japanese-American subjects with open-angle glaucoma or ocular hypertension in the United States

Study Number:
AR-13324-CS205

Study Phase:
2

Primary Objective(s):
In this Phase 2 study, the primary objectives are to evaluate:

- The ocular hypotensive efficacy of netarsudil ophthalmic solution relative to its placebo over a 28-day period
- The ocular and systemic safety of netarsudil ophthalmic solution relative to its placebo over a 28-day period

Secondary Objective(s):
None.

Study Design:
This will be a 28-day, double-masked, randomized, multicenter, placebo-controlled, parallel group efficacy and safety trial evaluating reduction of elevated intraocular pressure (IOP) with netarsudil ophthalmic solution. The purpose of this study is to assess the efficacy and safety of netarsudil ophthalmic solution (0.02% and 0.04%) compared to its placebo in Japanese or Japanese-American subjects that are at least 18 years of age with open-angle glaucoma (OAG) or ocular hypertension (OHT).

All investigational products will be dosed in both eyes (OU) once daily (QD) in the evening (PM). Subjects eligible to be enrolled in this study will be those of Japanese ethnicity within the second generation, with a diagnosis of either OAG or OHT that are on treatment with a topical ocular hypotensive medication. Approximately 180 subjects will be enrolled in this study. Subjects who agree to participate in this study and are enrolled will attend a total of 6 study visits: a Screening Visit, Qualification Visit #1, Qualification Visit #2/Day 1 (baseline), Week 1 (Day 8), Week 2 (Day 15), and Week 4 (Day 29).

Subjects currently using ocular hypotensive medications will be required to washout of their pre-study ocular hypotensive medication for a prescribed period (i.e., 5 days to at least 4 weeks, depending on the medication) prior to attending Qualification Visit #1. Subjects eligible to be enrolled in this study must meet all inclusion criteria and none of the exclusion criteria at each of the Screening Visit and Qualification Visits #1 and #2. Subjects will receive a baseline eye examination including IOP measurements at the Screening Visit and Qualification Visits #1 and #2 and, if deemed eligible, will be enrolled at Qualification Visit #2 and assigned to placebo or 1 of 2 investigational products in a 1:1:1 ratio according to a computer-generated randomization list. Randomization will take place using IWRS methodology and will stratify subjects by site.

Randomized subjects will dose the assigned investigational product in both eyes QD in the evening (between 20:00 and 22:00 hours) beginning on Day 1 and up to and including the evening prior to the final visit at

Visit 6 (Week 4). Procedures conducted at each of study Visits 4-6 will include safety measures and efficacy measurements, including IOP assessments. At Visits 4-6 (Weeks 1, 2, and 4, respectively), IOP will be assessed at 08:00, 10:00 and 16:00 hours. Following completion of the Visit 6 (Week 4) study visit procedures, subjects will exit the study. For subjects who discontinue early, every possible effort will be made to assure there is a final visit that includes all examinations listed for Visit 6.0 (Week 4) and dilated ophthalmoscopy.

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. Be of Japanese ethnicity within the second generation proven by birth certificate or family tree. Japanese generation is defined as follows: 1st generation is defined as born in Japan, immigrated to US; 2nd generation is defined as parents are 1st generation, however, the subject was born in US as an American citizen
3. Diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes (OAG in one eye and OHT in the fellow eye is acceptable)
4. Medicated intraocular pressure (IOP) ≥ 15 mmHg and < 30 mmHg in both eyes at screening visit (this also applies to treatment naïve subjects)
5. For OAG eyes, unmedicated (post washout) IOP ≥ 15 mmHg and < 35 mmHg in the study eye at 2 qualification visits (08:00 hour), 2-7 days apart. At second qualification visit IOP ≥ 15 mmHg and < 35 mmHg at 10:00 and 16:00 hours (in the same eye). [redacted]
6. For OHT eyes, unmedicated (post washout) IOP ≥ 22 mmHg and < 35 mmHg in the study eye at 2 qualification visits (08:00 hour), 2-7 days apart. At second qualification visit IOP ≥ 22 mmHg and < 35 mmHg at 10:00 and 16:00 hours (in the same eye). [redacted]
7. Best corrected visual acuity + 1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye)
8. Be able and willing to give signed informed consent and follow study instructions

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 (e.g., corneal edema, uveitis, or 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 up to 8 weeks is not judged safe as it would put the subject at risk for further vision loss
2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Shaffer Grade 2 or less). Note: Previous laser peripheral iridotomy is NOT acceptable
3. Intraocular pressure ≥ 35 mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification)
4. Ocular hyperemia score of moderate (+ 2) at Qualification Visit #2
5. Previous glaucoma intraocular surgery, including selective laser trabeculoplasty (SLT) or argon laser trabeculoplasty (ALT) in either eye
6. Refractive surgery in either eye (e.g., radial keratotomy, photorefractive keratectomy [PRK], laser-assisted in situ keratomileusis [LASIK], corneal cross-linking)
7. Ocular trauma within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening
8. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically

significant blepharitis, conjunctivitis, keratitis, or a history of herpes simplex or zoster keratitis in either eye at screening

9. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, 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), c) lubricating drops for dry eye (which may be used throughout the study), or d) non-steroid allergy drops (note: must not contain a vasoconstrictor) as prescribed by the Investigator
10. Mean central corneal thickness using optical pachymetry greater than 620 μm in either eye at screening
11. Any abnormality preventing reliable applanation tonometry of either eye (e.g., keratoconus)
12. Known hypersensitivity to benzalkonium chloride or excipients of netarsudil ophthalmic solution

Systemic:

13. Clinically significant abnormalities in laboratory tests at screening
14. Clinically significant systemic disease which might interfere with the study
15. Participation in any investigational study within 30 days prior to screening
16. Systemic medication that could have a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid-containing drug regardless of route of administration
17. 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 1 year post-menopausal or 3 months post-surgical sterilization All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study

Study Population:

A total of approximately 180 Japanese/Japanese-American subjects will be enrolled in this study at approximately 35 investigational sites in the US comprising a total of 60 subjects per treatment arm for each of the 3 treatment arms. Subjects will be at least 18 years of age with diagnosed OAG or OHT, each of whom meets all inclusion criteria and none of the exclusion criteria.

Investigational Product, Dose, and Mode of Administration:

- Netarsudil Ophthalmic Solution 0.02%, 1 drop QD (PM), OU
- Netarsudil Ophthalmic Solution 0.04%, 1 drop QD (PM), OU
- Netarsudil Ophthalmic Solution Placebo, 1 drop QD (PM), OU

Duration of Treatment:

Dosing will continue daily for 28 days continuously.

Efficacy Assessments:

The primary efficacy outcome will be the comparison of netarsudil ophthalmic solutions (0.02% and 0.04%) relative to placebo for mean diurnal IOP within a treatment at Week 4 (Day 29) by Goldmann Applanation Tonometry.

Secondary efficacy outcomes will be comparison of netarsudil ophthalmic solutions relative to placebo for:

- Mean diurnal IOP at Weeks 1 and 2 (Days 8 and 15, respectively)
- Mean change from baseline in mean diurnal IOP at each post-treatment visit
- Mean percent change from baseline in mean diurnal IOP at each post-treatment visit
- Mean IOP at each post-treatment time point
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point

- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in mean diurnal IOP levels

Other secondary efficacy analyses may be carried out as described in the study Statistical Analysis Plan.

Safety Assessments:

The primary safety measures in both eyes of enrolled subjects will include:

- Ocular symptoms/adverse events
- Best corrected visual acuity
- Objective findings of biomicroscopic examinations (i.e., anterior segment examinations including evaluation of cornea, conjunctiva, lids, and lens)
- Dilated ophthalmoscopy, including vertical cup-disc ratio measurements

Other safety assessments will be:

- Systemic safety assessments as measured by heart rate, blood pressure, and clinical laboratory evaluations (including hematology, clinical chemistry, and urinalysis)
- Pregnancy testing (for women of child bearing potential)

Statistical Methods:

The primary efficacy endpoint is the mean diurnal IOP across subjects within treatment group at Week 4. Assuming a two-sided test with alpha = 0.05 and a common standard deviation (SD) of 3.5 mmHg at each time point yielding a common SD of 3.0 for the diurnal mean assuming a correlation among time points of 0.60, 49 ITT subjects per arm yields at least 90% power to demonstrate superiority of netarsudil (0.02% or 0.04%) to placebo in mean diurnal study eye IOP (average of 08:00, 10:00, and 16:00 hours) at the Week 4 Visit assuming a difference of at least 2.0 mmHg in the mean diurnal IOP. The study will be considered a success and superiority of netarsudil to placebo will be concluded if the two-sided p-value ≤ 0.05 at Week 4. With 60 ITT subjects per arm, each test has 95% power to demonstrate superiority of netarsudil (0.02% or 0.04%) to placebo.

The primary analysis of the primary outcome will employ a linear model with mean diurnal IOP at Week 4 as the response, baseline mean diurnal IOP as a covariate, and treatment as a main effect factor, using the intent to treat population with Monte Carlo Markov Chain multiple imputation techniques used to impute missing data. The least squares mean differences (netarsudil – placebo) will be presented separately for netarsudil 0.02% and 0.04% as well as 2-sided p-values and 95% confidence intervals (CIs). Inference will be made on the 2-sided p-values. Superiority for a concentration (0.02% and 0.04%) will be concluded if the 2-sided p-value, for testing the difference (netarsudil – placebo) to 0, ≤ 0.05 and the point estimate of the difference < 0 at Week 4 for that concentration.

There will be no adjustment for the multiplicity of the 2 active concentrations (0.02% and 0.04%) tested against placebo in this Phase 2 study.

Date of Original Approved Protocol (Rev 0): 17 July 2017

Date of Most Recent Protocol Amendment (if applicable): Not applicable.

Prepared in: Microsoft Word 2016

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
A/G	Albumin/globulin
ALT	Argon Laser Trabeculoplasty
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCVA	Best Corrected Visual Acuity
BP	Blood Pressure
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
DHHS	Department of Health and Human Services
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LASIK	Laser-Assisted In Situ Keratomileusis
LDPE	Low Density Polyethylene
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
mmHg	Millimeters of Mercury
MedDRA	Medical Dictionary for Regulatory Activities

OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
OTC	Over-the-Counter
OU	Both Eyes
PM	Evening
PP	Per Protocol
PRK	Photorefractive Keratectomy
PT	Preferred Term
QD	Once Daily
ROCK	Rho Kinase
Rx	Medical Prescription
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SAS	Statistical Analysis Software
SD	Standard Deviation
SITA	Swedish Interactive Thresholding Algorithm
SLT	Selective Laser Trabeculoplasty
SOC	System Organ Class
SOP	Standard Operating Procedure
SSAR	Serious Suspected Adverse Reaction
SUSAR	Serious Unexpected Suspected Adverse Reaction
UA	Urinalysis
US	United States

1. INTRODUCTION

1.1 Investigational Product

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness. A major risk factor for glaucomatous visual field loss is elevated intraocular pressure (AGIS 2000).

The need for improved efficacy of glaucoma medications is supported by several clinical studies. Studies such as the Early Manifest Glaucoma Trial (Heijl 2002), the Ocular Hypertension Treatment Study (Kass 2002; Kass 2010), and the Collaborative Normal Tension Glaucoma Study Group (Collaborative Normal-Tension Glaucoma Study Group 1998) support the general conclusion that every millimeter of reduction in intraocular pressure (IOP) is significant for delaying disease progression. This conclusion holds true not only for high risk ocular hypertensive and glaucoma subjects with elevated IOPs but also for glaucoma subjects with IOPs in the normal range. Thus, the goal for treating subjects should be to lower IOP to the point that it prevents further damage to the optic nerve and achieve this without sacrificing safety or convenience.

Inhibitors of Rho kinase (ROCK) have emerged as a new class of IOP-lowering agents and are currently being tested in the clinic (Chen 2011; Kopczynski 2014). Netarsudil mesylate (AR-13324) is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. for topical ophthalmic use for lowering IOP. In both rabbit and monkey studies, netarsudil produces large reductions in IOP with a longer duration of action than reported for previously characterized Rho kinase inhibitors. Netarsudil ophthalmic solution has been shown to provide significant IOP lowering when dosed once-daily (QD) in the evening (Clinical Study Reports AR-13324-CS202, AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304), and reduces IOP potentially through several mechanisms: increasing trabecular outflow (Clinical Study Report AR-13324-CS102; Wang 2015), decreasing aqueous humor production (Clinical Study Report AR-13324-CS102; Wang 2015), and reducing episcleral venous pressure (Clinical Study Report AR-13324-CS102; Kiel 2015). The ability to reduce aqueous production may be related to netarsudil *in vitro* inhibitory activity against monoamine transporters, including the norepinephrine transporter.

The present study is a Phase 2 efficacy and safety study comparing netarsudil ophthalmic solution 0.02% and 0.04% to its placebo administered QD over the course of 28 days. This study will run concurrently with a Phase 1 ocular and systemic safety study comparing netarsudil ophthalmic solution 0.02% and 0.04% to its placebo after a single dose and daily QD dosing over a 7-day period (Protocol AR-13324-CS104). Both studies will recruit subjects with Japanese ethnicity within the second generation in the US.

1.2 Findings from Non-clinical and Clinical Studies

Non-clinical

Proof of concept for netarsudil in lowering IOP was established in primary pharmacology studies in 2 species, rabbits and monkeys. Safety pharmacology (central nervous system, respiratory, and cardiovascular) of netarsudil was investigated in rats and dogs. Pharmacokinetics/bio distribution of netarsudil was assessed after systemic and ocular administration of netarsudil. Ocular toxicity was investigated in studies up to 6 months in rabbits and up to 9 months in monkeys. Repeated dose toxicity of systemically administered netarsudil was investigated in studies up to 28 days in rats and dogs. Reproductive toxicity was investigated in rats and rabbits. The non-clinical program for netarsudil also included a standard range of genotoxicity tests.

Clinical

The clinical development of netarsudil ophthalmic solution includes pharmacokinetics, tolerability, and dose-response investigations. The assessment of the ocular and systemic safety of netarsudil ophthalmic solution 0.02% in two Phase 1 clinical studies (Clinical Study Reports AR-13324-CS101 and AR-13324-CS102) has been completed. Results from a previous Phase 2 study (Clinical Study Report AR-13324-CS201) investigating a range of netarsudil concentrations (0.01%, 0.02%, and 0.04%) were used to select the appropriate concentrations of netarsudil ophthalmic solution to be tested in the present study (0.02% and 0.04%). Three well-controlled Phase 3 clinical studies (Clinical Study Reports AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304) evaluating the safety and efficacy netarsudil ophthalmic solution 0.02% have been completed.

Detailed information on nonclinical and clinical studies completed with netarsudil ophthalmic solution is provided in the Investigator's Brochure.

1.3 Risks and Benefits to Human Subjects

As no other compounds of this class are approved, and only early stage clinical experience is available, the risks and benefits are not well understood at this time. Given the pharmacology of this class of agents and the results of previous Phase 1, Phase 2, and Phase 3 clinical studies by the Sponsor (Clinical Study Reports AR-13324-CS101, AR-13324-CS102, AR-13324-CS201, AR-13324-CS202, AR-13324-CS301, and AR-13324-CS302, and AR-13324-CS304), it is expected that transient hyperemia of the conjunctiva will be observed. The reader should refer to the Investigator's Brochure for more detailed information on potential risks due to use of netarsudil ophthalmic solution.

The major potential benefit from exposure to netarsudil ophthalmic solution is reduction in IOP in subjects with open angle glaucoma (OAG) or ocular hypertension (OHT). A long-term benefit of reduced IOP could be slowing of disease progression and preservation of vision in subjects when measured over periods of months to years

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

In this Phase 2 study, the primary objectives are to evaluate:

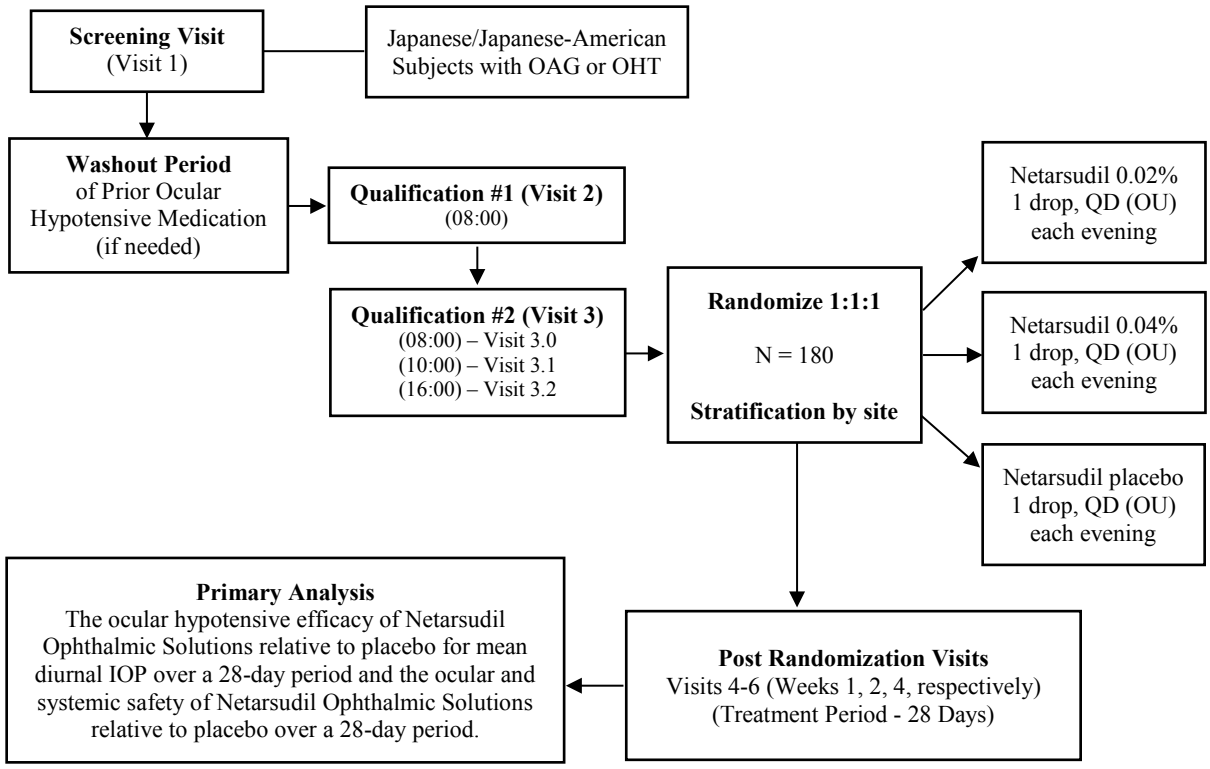
- The ocular hypotensive efficacy of netarsudil ophthalmic solution relative to its placebo over a 28-day period
- The ocular and systemic safety of netarsudil ophthalmic solution relative to its placebo over a 28-day period

2.2 Secondary Objective(s)

None.

3. INVESTIGATIONAL PLAN

Figure 1 Study Design



3.1 Overall Study Design and Plan

This will be a 28-day, double-masked, randomized, multicenter, placebo-controlled, parallel-group efficacy and safety trial evaluating reduction of elevated IOP with netarsudil ophthalmic solution. The purpose of this study is to assess the efficacy and safety of netarsudil ophthalmic solution (0.02% and 0.04%) compared to its placebo in Japanese or Japanese-American subjects that are at least 18 years of age with OAG or OHT.

All investigational products will be dosed in both eyes (OU) QD in the evening (PM). Subjects eligible to be enrolled in this study will be those of Japanese ethnicity within the second generation, with a diagnosis of either OAG or OHT that are on treatment with a topical ocular hypotensive medication. Approximately 180 subjects will be enrolled. Subjects who agree to participate in this study and are enrolled in the study will attend a total of 6 study visits: a Screening Visit, Qualification Visit #1, Qualification Visit #2/Day 1 (baseline), Week 1 (Day 8), Week 2 (Day 15), and Week 4 (Day 29).

Subjects currently using ocular hypotensive medications will be required to washout of their pre-study ocular hypotensive medication for a prescribed period (i.e., 5 days to at least 4 weeks, depending on the medication) prior to attending Qualification Visit #1. Subjects

eligible to be enrolled in this study must meet all inclusion criteria and none of the exclusion criteria at each of the Screening Visit and Qualification Visits #1 and #2. Subjects will receive a baseline eye examination including IOP measurements at the Screening Visit and Qualification Visits #1 and #2 and, if deemed eligible, will be enrolled at Qualification Visit #2 and assigned to placebo or 1 of 2 investigational products in a 1:1:1 ratio according to a computer-generated randomization list. Randomization will take place using Interactive Web Response System (IWRS) methodology and will stratify subjects by site.

Randomized subjects will dose the assigned investigational product in both eyes QD in the evening (between 20:00 and 22:00 hours) beginning on Day 1 and up to and including the evening prior to the final visit at Visit 6 (Week 4). Procedures conducted at each of study Visits 4-6 will include safety measures and efficacy measurements, including IOP assessments. At Visits 4-6 (Weeks 1, 2, and 4, respectively), IOP will be assessed at 08:00, 10:00 and 16:00 hours. Following completion of the Visit 6 (Week 4) study visit procedures, subjects will exit the study. For subjects who discontinue early, every possible effort will be made to assure there is a final visit that includes all examinations listed for Visit 6.0 (Week 4) and dilated ophthalmoscopy.

3.2 Rationale for Study Design and Control Group

In order to further evaluate the hypotensive efficacy of netarsudil ophthalmic solution relative to its placebo in subjects with OAG or OHT and to generate additional safety data for netarsudil, a double-masked, parallel group, 3-arm active- and placebo-controlled study design was selected.

As the intended route of administration for netarsudil ophthalmic solution is topical ocular, this is the route to be used in this study. The dosage regimen selected for this study is based on a previously completed Phase 2 study (AR-13324-CS202) and 3 completed Phase 3 studies (AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304).

Efficacy and safety results with netarsudil ophthalmic solution to date have been generated in a mostly non-Japanese population. In order to ensure that similar results are observed in Japanese subjects, this study is being conducted in subjects of Japanese ethnicity.

3.3 Expected Duration of Subject Participation

Each subject is planned to undergo a minimum washout period of their current ocular hypotensive medications (if needed), followed by approximately 28 days of treatment. Treatment duration with the investigational product (IP) for this study will start on the evening of Visit 3 (Qualification Visit #2; Day 1) and end on the evening before Visit 6 (Week 4/Day 28).

4. STUDY POPULATION SELECTION

4.1 Study Population

A total of approximately 180 Japanese/Japanese-American subjects will be enrolled in this study at approximately 35 investigational sites in the US comprising a total of 60 subjects per treatment arm for each of the 3 treatment arms. Subjects will be at least 18 years of age with diagnosed OAG or OHT, each of whom meets all inclusion criteria and none of the exclusion criteria.

Planned enrollment numbers are higher (180 total, 60 subjects per arm) than statistically required for demonstrating efficacy (approximately 49 intent-to-treat [ITT] subjects per arm for 90% power) to account for the potential for subjects who do not complete the entire dosing period, or who have disqualifications. Over-enrollment (beyond 180 subjects) is to be undertaken only after communication between the investigational site and the Sponsor representative.

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. Be of Japanese ethnicity within the second generation proven by birth certificate or family tree. Japanese generation is defined as follows: 1st generation is defined as born in Japan, immigrated to US; 2nd generation is defined as parents are 1st generation, however, the subject was born in US as an American citizen

3. Diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes (OAG in one eye and OHT in the fellow eye is acceptable)

4. Medicated intraocular pressure (IOP) $\geq$ 15 mmHg and < 30 mmHg in both eyes at screening visit (this also applies to treatment naïve subjects)

5. For OAG eyes, unmedicated (post washout) IOP $\geq$ 15 mmHg and < 35 mmHg in the study eye at 2 qualification visits (08:00 hour), 2-7 days apart. At second qualification visit IOP $\geq$ 15 mmHg and < 35 mmHg at 10:00 and 16:00 hours (in the same eye). [redacted]

6. For OHT eyes, unmedicated (post washout) IOP $\geq$ 22 mmHg and < 35 mmHg in the study eye at 2 qualification visits (08:00 hour), 2-7 days apart. At second qualification visit IOP $\geq$ 22 mmHg and < 35 mmHg at 10:00 and 16:00 hours (in the same eye) [redacted]

7. Best corrected visual acuity + 1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye)

8. Be able and willing to give signed informed consent and follow study instructions

4.3 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 (e.g., corneal edema, uveitis, or 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 up to 8 weeks is not judged safe as it would put the subject at risk for further vision loss

2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Shaffer Grade 2 or less). Note: Previous laser peripheral iridotomy is NOT acceptable

3. Intraocular pressure ≥ 35 mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification)

4. Ocular hyperemia score of moderate (+ 2) at Qualification Visit #2

5. Previous glaucoma intraocular surgery, including selective laser trabeculoplasty (SLT) or argon laser trabeculoplasty (ALT) in either eye

6. Refractive surgery in either eye (e.g., radial keratotomy, photorefractive keratectomy [PRK], laser-assisted in situ keratomileusis [LASIK], corneal cross-linking)

7. Ocular trauma within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening

8. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, or a history of herpes simplex or zoster keratitis in either eye at screening

9. Use of ocular medication in either eye of any kind within 30 days of screening and throughout the study, 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), c) lubricating drops for dry eye (which may be used throughout the study), or d) non-steroid allergy drops (note: must not contain a vasoconstrictor) as prescribed by the Investigator

10. Mean central corneal thickness using optical pachymetry greater than 620 μm in either eye at screening

11. Any abnormality preventing reliable applanation tonometry of either eye (e.g., keratoconus)

12. Known hypersensitivity to benzalkonium chloride or excipients of netarsudil ophthalmic solution

Systemic:

13. Clinically significant abnormalities in laboratory tests at screening

14. Clinically significant systemic disease which might interfere with the study

15. Participation in any investigational study within 30 days prior to screening

16. Systemic medication that could have a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid-containing drug regardless of route of administration

17. 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 1 year post-menopausal or 3 months post-surgical sterilization All females of childbearing potential must have a negative urine 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 Study Drug

Netarsudil mesylate (AR-13324) Ophthalmic Solution is a sterile, isotonic, buffered aqueous solution containing netarsudil (0.02% or 0.04%), boric acid, mannitol, water for injection, and preserved with benzalkonium chloride [redacted]. [redacted]

5.1.2 Placebo or Control Drug

Netarsudil ophthalmic solution placebo is a sterile, isotonic, buffered aqueous solution containing boric acid, mannitol, water for injection, and preserved with benzalkonium chloride [redacted]. [redacted]

5.2 Treatments Administered

Subjects will be randomized to receive IP netarsudil ophthalmic solution (0.02% or 0.04%) or its placebo administered OU. Subjects will instill 1 drop into each eye QD in the evening between 20:00 and 22:00 hours. IP doses will be administered by the study subjects. For subjects deemed unable to self-administer the doses, a guardian or alternative caregiver will be asked to administer the medication. All subjects will administer study treatment for approximately 28 days.

5.3 Selection and Timing of Dose for Each Patient

The study drug doses and treatment period selected for this study are based on one Phase 1 study (AR-13324-CS101) and the positive outcomes seen for netarsudil in 2 previously completed Phase 2 studies (AR-13324-CS201 and AR-13324-CS202) and 3 completed Phase 3 studies (AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304). Each dose is being administered QD OU in the evening (between 20:00 and 22:00 hours) in this study, since this dosing regimen was found to provide good efficacy and tolerability in the previous clinical studies.

5.4 Method of Assigning Patients to Treatment Groups

A randomization code for allocating the treatments will be prepared by an independent biostatistician who is not involved in the day-to-day conduct of the study. Subjects will be randomized using IWRS in a 1:1:1 ratio to receive netarsudil ophthalmic solution (0.02% or 0.04%) or its placebo and will stratify subjects by site.

5.5 Masking

Treatment assignments will be masked to the Investigator, the clinical study team (Sponsor, personnel involved in day to day study management, Monitors, Data Managers, and

Statisticians), and the subjects for the duration of the study. Only in case of medical emergency or occurrence of AEs that warrant unmasking in the opinion of the Investigator, will the treatment assignment(s) be unmasked and made available to the Investigator and the Sponsor Medical Monitor or designee. Individual unmasking by the Investigator will normally result in withdrawal of the subject from the study and should only be performed for the specific subject requiring unmasking in their treatment group. In the absence of medical need, the randomization code will not be available to the above personnel until after the study is completed and the database is unlocked.

If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the Investigator should contact the Sponsor Medical Monitor or designee. After consultation with the Sponsor Medical Monitor or designee, a decision will be made as to whether or not the treatment should be unmasked. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on the remaining subjects.

If there is an emergency situation in which treatment of an AE requires immediate unmasking, and the Investigator is unable to contact the Sponsor Medical Monitor or designee, the Investigator may unmask the treatment. The Investigator will perform the unmasking through the IWRS or other randomization system. In the case of such unmasking in an emergency situation, the Investigator should contact the Sponsor immediately and document unmasking in writing, recording the date, time, and reason for unmasking the study drug treatment in the source documentation.

5.6 Concomitant Therapy

As noted in Section 5.7.1, subjects using ocular hypotensive medications at screening are required to undergo a washout of their current ocular hypotensive medications. 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)
- α-adrenoceptor agonists
- β- adrenoceptor antagonists
- Muscarinic agonists (e.g., pilocarpine)

- Prostaglandin analogues

- Any corticosteroid containing ocular or systemic drug is disallowed during the study regardless of route of administration

Systemic therapy with agents other than corticosteroids that could have an effect on IOP is to be consistent in dose, regimen and agent within the 30 days prior to screening and throughout the study. For example, a subject can be treated with a systemic β-adrenoceptor antagonist as long as the particular agent and its dose and regimen had been consistent for the 30 days prior to screening, and there is no reason to believe that alteration would be necessary at some point later during the study. Subjects should be cautioned to avoid use of alcohol or the use of any drugs such as cannabis or marijuana during the study visit days.

Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses at least 30 minutes before instillation of study medication, and not place them in their eye(s) until 30 minutes after instillation.

Use of all medications should be documented on the appropriate case report form (CRF). Investigators are encouraged to contact the Sponsor/Sponsor representative for any questions regarding allowed medications. 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 Sponsor.

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., fluorescein and local anesthetic) will be allowed, and individual documentation not required. Any change in dosing parameters should also be recorded in the CRF.

5.7 Restrictions

5.7.1 Prior Therapy/Washout Period

Subjects currently using ocular hypotensive medications must undergo a minimum washout period as specified in Table 1.

If washout is to be extended beyond 8 weeks (56 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
β-adrenoceptor antagonists	4 weeks
Adrenergic agonists (including α-agonists such as brimonidine and apraclonidine)	2 weeks
Muscarinic agonists (e.g., pilocarpine), carbonic anhydrase inhibitors (topical or oral)	5 days

Hughes 2005

5.7.2 Fluid and Food Intake

On days that diurnal IOP measurements are made, subjects may not consume alcohol. Otherwise, there are no general restrictions on fluid or food intake for subjects participating in this study.

5.7.3 Subject Activity Restrictions

On days that diurnal IOP measurements are made, subjects may not engage in strenuous activity. Otherwise, there are no restrictions on subject activities during their participation in this study.

5.8 Treatment Compliance

All subjects will be instructed on the importance of following the once-daily dosing regimen. Dosing should occur in the evening between 20:00 and 22:00 hours. As no commercially available method is readily available for direct, single-container monitoring of treatment adherence with multi-dose ophthalmic products, no formal measure of treatment compliance is planned. Subjects should be reminded at all visits to dose every evening. In addition, subjects will be provided with dosing reminders.

5.9 Packaging and Labeling

The container-closure system for the netarsudil ophthalmic solution (0.02% or 0.04%) and netarsudil ophthalmic solution placebo in this clinical study is a white, multi-dose low density polyethylene (LDPE) dropper dose ophthalmic bottle with a polypropylene white cap. Each packaged unit will be labeled with an investigational label with the following minimal information: the study number, kit number, and storage statement, including a statement “For Use in Clinical Study Only. Caution: New Drug - Limited By Federal (US) Law to Investigational Use.” or equivalent.

The products for each individual treatment assignment will be packaged into identical subject kits; each subject kit will contain one of 3 treatments: netarsudil ophthalmic solution 0.02% or 0.04% or netarsudil ophthalmic solution placebo.

5.10 Storage and Accountability

The study treatments must be dispensed or administered according to the procedures prescribed in this protocol. Only subjects enrolled in the study may receive study treatment, in accordance with all the applicable regulatory requirements. Only authorized staff is allowed to dispense these medications.

Under normal conditions of handling and administration, the study treatments are not expected to pose significant safety risk to site staff. Adequate precautions must be taken to avoid direct contact with the study treatment.

The study treatments will be stored in a secure area under the appropriate physical conditions for the product. Access to the study treatment will be limited to authorized site staff only. The study treatments will be stored as directed on the drug label. The study treatments should be stored refrigerated (2°C to 8°C/36°F to 46°F). Temperature of the study treatment storage location at the site is to be monitored using a calibrated monitoring device and documented.

At time of dispensing, the subject will be instructed to store the bottle(s) as directed on the drug label and to keep the bottle(s) refrigerated (2°C to 8°C/36°F to 46°F). Subjects should be instructed not to freeze the product.

5.11 Investigational Product Retention at Study Site

5.11.1 Receipt and Disposition of Study Medication

Study medication will be shipped to the Investigator's site from a central depot. The study medication storage manager 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 study medication. The responsible person will also maintain the drug accountability records.

5.11.2 Return of Study Medication

When the site is closed, the study is completed, or is terminated by the Sponsor; all study material including used and unused study medication will be returned to the Sponsor (or its 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 study medication. The study medication storage manager or designee 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 to the Sponsor's designee.

6. STUDY PROCEDURES

6.1 Informed Consent

Prior to any study procedures, the study will be discussed with each subject. 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.

The informed consent form (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 ICF must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject is exposed to 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 Demographics and 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 will also 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 Physical Examination

The Investigator will review each subject's medical and ophthalmic history including systemic and ocular medication use to determine eligibility for this study. If enrolled, the Investigator will determine if there are any changes in health or concomitant medication use at each follow-up visit.

The Investigator or designee will also perform the following ophthalmic assessments as described in Appendix 2: visual acuity, visual field, IOP, biomicroscopy, central corneal thickness, gonioscopy, symptomatology, and dilated ophthalmoscopy.

6.4 Vital Signs

The Investigator or designee will measure heart rate, pulse, and blood pressure as described in Appendix 2.

6.5 Clinical Laboratory Tests

6.5.1 Laboratory Parameters

A chemistry panel, complete blood count (hematology and differential), and urinalysis will be performed as shown.

Note that fasting will NOT be required and specific values may be out of the typical fasting range.

The clinical laboratory results must be reviewed by the Investigator prior to subject enrollment, and the tests CANNOT be indicative of any clinically significant disease in the opinion of the Investigator.

6.5.2 Sample Collection, Storage and Shipping

The site staff responsible for collecting the laboratory samples will be identified on the Delegation of Responsibilities Log. The laboratory responsible for processing the sample collections is [redacted]. Details for the preparation and shipment of samples and reference ranges will be provided in the laboratory manual.

6.5.3 Pregnancy Testing

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

The Sponsor will provide urine pregnancy tests to the sites. Expiration dates on the pregnancy tests will be reviewed and confirmed by the site prior to use.

If a female becomes pregnant during the study, the Investigator should notify the Sponsor immediately after the pregnancy is confirmed and the subject will be exited from the study. The Investigator should follow the progress of the pregnancy until the fetus is carried to term.

6.6 Dispensing Investigational Product

Study staff responsible for dispensing study medication will be listed on the Delegation of Responsibilities Log. When a subject meets all criteria for selection and has completed all screening assessments, the subject will be assigned to a treatment group according to the

IWRS. The responsible study staff will account for used and unused investigation product by maintaining a study medication accountability log.

6.7 Efficacy Assessments

6.7.1 Specification of the Efficacy Parameters

The primary efficacy outcome will be the comparison of netarsudil ophthalmic solution (0.02% and 0.04%) relative to placebo for mean diurnal IOP within a treatment at Week 4 (Day 29) by Goldmann Applanation Tonometry. A description of the method for measuring IOP to be used in this study is contained in Appendix 2.

Secondary efficacy outcomes will be comparison of netarsudil ophthalmic solution relative to placebo for:

- Mean diurnal IOP at Weeks 1 and 2 (Days 8 and 15, respectively)
- Mean change from baseline in mean diurnal IOP at each post-treatment visit
- Mean percent change from baseline in mean diurnal IOP at each post-treatment visit
- Mean IOP at each post-treatment time point
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in mean diurnal IOP levels

Other secondary efficacy analyses may be carried out as described in the study Statistical Analysis Plan.

6.7.2 Method and Timing for Assessing, Recording, and Analyzing of Efficacy Parameters

As detailed in subsequent sections describing each visit and Appendix 1, IOP will be measured at a screening visit, at 2 qualification visits after washout of ocular hypotensive medications as required, and at each post Day 1 treatment study visit.

6.8 Safety Assessments

The primary safety measures in both eyes of enrolled subjects will include:

- Ocular symptoms/adverse events

- Best corrected visual acuity

- Objective findings of biomicroscopic examinations (i.e., anterior segment examinations including evaluation of cornea, conjunctiva, lids, and lens)

- Dilated ophthalmoscopy, including vertical cup-disc ratio measurements

Other safety assessments will be:

- Systemic safety assessments as measured by heart rate, blood pressure, and clinical laboratory evaluations (including hematology, clinical chemistry, and urinalysis)

- Pregnancy testing (for women of child bearing potential)

6.9 Adverse Events Assessments

6.9.1 Performing Adverse Event (AE) Assessments

Qualified study staff responsible for assessing adverse events (AEs) will be listed on the Delegation of Responsibilities Log. This includes assessment of AE severity and relationship to study medication. Adverse event information may be volunteered by the subject or solicited by study personnel through non-leading questions.

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF. Adverse events should be documented from the time the subject receives the first dose of study medication until 30 days after the last dose of study drug.

If a subject has an ongoing AE at the time of study completion, the ongoing AE must be followed-up and provided appropriate medical care until the event has resolved or stabilized.

Documentation of AEs/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome.

6.9.2 Adverse Event Definition

The following definitions of terms apply to this section:

- *Adverse event*. Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- *Life-threatening AE or life-threatening suspected adverse reaction (SAR)*. An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

- *Serious adverse event (SAE) or serious suspected adverse reaction (SSAR)*. An AE or SAR is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, subject hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability 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 and 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 subject hospitalization, or the development of drug dependency or drug abuse.

- *Suspected adverse reaction (SAR)* means any AE for which there is a reasonable possibility that the drug caused the AE. For the 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 adverse event caused by a drug.

- *Unexpected AE or unexpected SAR*. An AE or SAR is considered ‘‘unexpected’’ if it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Note: Any medical condition present prior to administration of the masked study medication which remains unchanged or improved should not be recorded as an AE at subsequent visits.

Note: If an event occurs during the washout period (prior to subject enrollment and the commencement of study medication), it should be recorded as part of the Medical History and not as an AE. As noted in Section 7.3.1, any change in their Visit 1 (Screening) health status prior to enrollment should be recorded on the Medical History page of the CRF.

Note: In the present study, Investigators are asked to use the verbatim term “conjunctival hyperemia” on the study AE form to describe observations of conjunctival redness if the ocular redness observation is increased from Visit 1 (Screening) observations and clinically meaningful. Investigators are also asked to note all observations of conjunctival hyperemia on the biomicroscopy CRF as well as on the study AE form.

6.9.3 Timing for Reporting of Adverse Events

The AEs occurring during the study must be documented, regardless of the assumption of a causal relationship. Adverse events should be documented from the time the subject receives the first dose of study medication until subject participation in the study has been completed. If a subject has 1 or more ongoing AEs at the time of study completion, the subject must be followed and provided appropriate medical care until the sign(s) and/or symptoms(s) of the AE have remitted or stabilized in the opinion of the Investigator.

When recording an AE, the following information should be provided on the study AE CRF:

1. Action Taken with Study Drug:

- None
- Investigational Product Discontinued
- Investigational Product Interrupted

2. 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

3. Outcome of an adverse event is coded as:

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

6.9.4 Severity

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

- 1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities
- 2 = Moderate: bothersome, discomfort sufficient to possibly 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 6.9.8 for further information on serious AEs [SAEs]).

6.9.5 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 factors such as subject's clinical condition; therapeutic interventions, concomitant disease or therapy administered to the subject and does not follow a known response pattern to the product.
- **Unlikely Related**: The event is most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.
- **Possibly Related**: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.
- **Related**: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study

medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

6.9.6 Expectedness

The most frequently reported AE for netarsudil ophthalmic solution in two Phase 2 and three Phase 3 studies (Clinical Study Reports AR-13324-CS201, AR-13324-CS202, AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304) has been conjunctival hyperemia. Other AEs seen in greater frequency with netarsudil than in active control treatment arms in these studies include instillation site erythema or pain, eyelid erythema, conjunctival hemorrhage, conjunctival vascular disorder, blurred vision, corneal deposits, eye irritation, increased lacrimation, and foreign body sensation.

An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator's Brochure as occurring with this class of drugs or as anticipated from the pharmacological properties of netarsudil, and are not specifically mentioned as occurring with the IP. The AEs that are both unexpected and serious should be reported in an expedited fashion to the Sponsor (see Section 6.9.8 for further details).

6.9.7 Clinical Laboratory Adverse Events

Clinical laboratory values (other than pregnancy test results) that are noted as abnormal and clinically significant at study exit and that are changes from Visit 1 (Screening) values will be documented as AEs.

6.9.8 Serious Adverse Events or Serious Suspected Adverse Events

An Investigator must immediately report any SAE or SSAR (see Section 6.9.2 for definitions) to the Sponsor or Sponsor representative (contact information below), whether or not the SAE or SSAR is considered drug-related, including those listed in the protocol or Investigator's Brochure. The Investigator report 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 study for a subject or any SAE or SSAR that occurs within 4 weeks (i.e., 30 days) after the last administration of study medication. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with Section 6.9.2 of the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor or Sponsor representative. 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 AEs that are serious, unexpected (i.e., not in the Investigator's Brochure) and judged related to the study medication, the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of notification or occurrence of the SAE.

Pregnancies occurring in subjects enrolled in the study or in their partners must be reported and followed to outcome. While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by the Sponsor or Sponsor representative. Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE. Other pregnancy complications should be reported as SAEs, if they meet serious criteria. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality.

The Investigator must complete the pregnancy report form and fax or email the form to the Sponsor or Sponsor representative within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the pregnancy report form is to be completed and submitted by fax or email to the Sponsor or Sponsor representative.

Pregnancies occurring up to 30 days after the last administration of study drug are to be reported.

Serious adverse events 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]

Medical Monitor/Sponsor Contact Telephone Number:
[redacted]

6.9.9 Follow-up of Subjects after Adverse Events

If an AE/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. If a serious or 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.

6.10 Concomitant Medication Assessments

Use of all medications should be documented on the appropriate CRF. The site staff responsible for recording all concomitant medications will be identified on the Delegation of

Responsibilities Log. Investigators are encouraged to contact the Sponsor/Sponsor representative for any questions regarding allowed medications. 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 Sponsor.

6.11 Best Corrected Visual Acuity (BCVA)

Best corrected visual acuity (BCVA) will be taken at visits as a measure of ocular function and will be measured at screening and frequently throughout the study. Visual acuity will be measured using ETDRS charts or their equivalents. Accepted charts are those designed according to the principles described by Ferris and coworkers (Ferris 1982) and supported by the guidelines from the Eye Care Technology Forum (Ferris 1996).

See Appendix 2 for details of the procedures to be followed when determining BCVA.

6.12 Biomicroscopy

Biomicroscopic examination of the eyelids, conjunctiva, cornea, anterior chamber, lens, iris, and pupil of both lenses will be carried out at every study visit for both eyes of subjects. Normal or abnormal status of these ocular tissues will be graded as described in Appendix 2.

6.13 Gonioscopy/Pachymetry

Gonioscopy will be used to confirm the iridocorneal angle is open and to what extent. Eligible subjects must have an angle of 3 or 4 (Shaffer grading scale; Stamper 2009) for participation in the study. Gonioscopy may be performed up to 3 months prior to randomization. Pachymetry will be used to measure the thickness of the central cornea. Both of these assessments will be done in order to determine the eligibility of a subject to be enrolled in this study. Further information on these procedures is found in Appendix 2.

6.14 Visual Field Testing

Visual field testing must be performed in both eyes. Visual field testing may be performed up to 3 months prior to randomization. Visual fields must be determined as automated threshold perimetry (e.g., 30-2 or 24-2 Humphrey). SITA Standard is preferred, SITA fast is also allowed. Visual fields must be reliable, defined as those with a) fixation losses less than or equal to 33%, b) false positives less than or equal to 33%, and c) false negatives less than or equal to 33%. Visual fields fixation losses should not be rounded up to the next whole number value. **The gaze track and blind spot should be turned on for all visual fields assessments in order to calculate the fixation losses.** See Appendix 2 for further information.

6.15 Dilated Ophthalmoscopy

A dilated funduscopic examination including evaluation of the retina, vitreous, macula, choroid, optic nerve, and vertical cup/disc ratio will be performed. See Appendix 2 for

further information on scoring. Evaluation of vertical cup-disc ratio will be performed when ophthalmoscopy is performed.

6.16 Intraocular Pressure

Local anesthetic will also be applied in order to facilitate IOP measurements with the Goldmann Applanation Tonometer. Tonometer calibration on at least a monthly basis must be documented.

Two consecutive IOP measurements of each eye must be obtained. If the 2 measurements differ by more than 2 mmHg, a third measurement must be obtained. Intraocular pressure will be analyzed as the mean of 2 measurements or as the median of 3 measurements (Sherwood 2006).

Each Goldmann tonometry value is read as an integer. When calculating the mean or median, it is possible to have a fractional value; any non-integral mean or median IOP number will be reported to one decimal place. Note: For purposes of determining eligibility of subjects to be enrolled, any non-integral mean IOP number should not be rounded.

IOP should be measured by qualified individuals using a calibrated Goldmann applanation tonometer.

6.17 Study Eye Selection Process

Subjects must qualify in both eyes based upon IOP and ocular history for a subject who qualifies; the study eye will be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye will be the study eye. For each subject, BOTH eyes will be treated.

6.18 Removal of Subjects from the Study or Study Treatment

6.18.1 Completed Subject

A completed subject is defined as one who completes all 28 days of planned dosing and completion of the post-treatment follow-up day visit procedures.

6.18.2 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, the Medical Monitor, 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 listed for Visit 6.0 (Day 29) as well as dilated ophthalmoscopy.

The subject may also be discontinued from the study for the following reasons:

- **Lack of Efficacy** (as demonstrated by IOP measurements and Investigator decision that there is a risk of additional glaucomatous damage if the subject continues in the study).

- **Adverse Events** (AEs including, in the opinion of the Investigator, clinically relevant laboratory abnormalities and intercurrent diseases reported by the subject or observed by the investigator with documentation in the CRF).

- **Withdrawal of Consent**

- **Non-compliance** (e.g., non-adherence to scheduled follow-up visits or non-compliance with dosing)

- **Lost to Follow-up**

- **Disallowed Concurrent Medication**

- **Investigator Decision**

- **Protocol Deviation**

- **Death**

- **Other**

6.18.3 Actions after Discontinuation

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

For subjects who choose to withdraw consent or who are discontinued for non-compliance prior to completing the study, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for Visit 6.0 (Exit) and dilated ophthalmoscopy.

6.18.4 Discontinuation of the Entire Study

The entire study may be discontinued at a given site (by the Investigator or the Sponsor/ Sponsor representative or at all sites by the Sponsor). Prompt, written notice of reasonable cause to all other relevant parties (Sponsor or Investigator) is required. Prompt notice to the IRB and to regulatory authorities is also required.

6.18.5 Completed Study

The study is completed when the planned enrollment has been completed, and all the enrolled subjects have completed the study. The Sponsor representative will be in communication with the Investigational sites regarding enrollment.

6.19 Appropriateness of Measurements

The ophthalmic and systemic measures used in this study are consistent with standard of care. In particular, IOP as measured by Goldmann applanation tonometry, the primary efficacy assessment in this study, is accepted worldwide as a standard for testing of pharmacologically active agents intended to reduce IOP.

7. STUDY ACTIVITIES

The schedule of study visits and procedures is shown in Appendix 1.

7.1 Visit 1 (Screening)

This visit may occur at any time of the day. The Investigator or a member of his/her 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 signed written informed consent must be obtained from the subject prior to any study specific procedures or assessments. The ICF process will be clearly documented in the subject's source.

Significant medical and ophthalmic history including concomitant medication use will be taken, and demographic measures recorded (see Section 6.2).

The following procedures will be performed (see Appendix 2 for procedure details):

- Heart rate and blood pressure
- Pregnancy test: All females of childbearing potential must have a negative urine pregnancy test result
- Best Corrected Visual Acuity
- Central corneal thickness will be measured by ultrasound pachymetry (taken at screening or within 1 week prior to the Screening Visit)
- Intraocular pressure (before pupil dilation): Medicated IOP must be ≥ 15 mmHg and < 30 mmHg in both eyes at the Screening Visit (this also applies to treatment naïve subjects)
- Biomicroscopy
- Dilated ophthalmoscopy (including vertical cup-disc ratio)
- Visual fields and gonioscopy may be taken up to 3 months prior to randomization in both eyes
- Symptomatology: Individuals will be asked "How are you feeling?"

Blood samples will be taken for clinical chemistry and hematology, and a urine sample will be taken for urinalysis (Appendix 2). The results of blood work and urinalysis should be reviewed after this study visit in order to determine eligibility of the subject prior to undertaking the examination at Visit 2 (Qualification Visit #1).

For subjects who are unable or unwilling to have blood drawn and urine collected for clinical labs at Visit 1 (Screening), the blood and urine sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available and reviewed for eligibility for that subject prior to Visit 3 (Qualification Visit #2).

The Investigator will evaluate the results of these examinations for possible enrollment of the individual into the study.

7.1.1 Evaluation of Eye-Drop Instillation Performance

Subjects (or legally authorized representative for subjects deemed unable to administer) will be provided a bottle of commercially available, multi-dose, non-medicated artificial tears in a room with access to water and soap. Medication instiller 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, guardian, or alternative person to assure that they instill 1 drop 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 (guardian or alternative person) 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.

7.1.2 Washout

As noted in Section 5.7.1, a washout period is required for individuals currently using ocular hypotensive medications and who meet the other qualifications for enrollment.

7.2 Visit 2 (Qualification Visit #1, for 08:00 hours IOP and safety measurements)

After the washout (if needed), individuals will return to the Investigator's office in the early morning. The subject will be questioned regarding any changes in their health or concomitant medication use. Any change in the individual's Visit 1 health status should be recorded on the Medical History page of the CRF (e.g., the subject has been diagnosed with cancer).

Inclusion/exclusion criteria will be reviewed again for the qualified individual. Results of the clinical laboratory tests from Visit 1 need to be available and reviewed by the Investigator.

For subjects who were unable or unwilling to have blood drawn and urine collected for the clinical labs at Visit 1, the blood and urine sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).

The following procedures will be performed:

- Heart rate and blood pressure

- Symptomatology: Individuals will be asked "How are you feeling?"

- Best Corrected Visual Acuity

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08:30 hours)

For further evaluation of OAG eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 15 mmHg and < 35 mmHg in both eyes. For further evaluation of OHT eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 22 mmHg and < 35 mmHg in both eyes. [redacted]

Individuals who do NOT meet the IOP requirements above may return for up to 2 additional qualification visits within 1 week of failing this qualification 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.

Individuals who screen fail due to IOP being ≥ 35 mmHg in either eye (exclusion criterion) MAY NOT return for additional qualification visits.

Qualified individuals will be scheduled to return 2-7 days later for the second qualification visit.

7.3 Treatment Period

7.3.1 Visit 3.0 (Qualification Visit #2, Day 1, for IOP and safety measurements at 08:00 hours)

Within 2 to 7 days after Visit 2, individuals will return to the Investigator's office for the next 08:00 hour IOP measurement.

The results of the clinical laboratory tests from Visit 1 need to be available, and reviewed by the Investigator. In order for the individual to be enrolled, the tests CANNOT be indicative of any clinically significant disease in the opinion of the Investigator.

The subject will be questioned regarding any changes in their health or concomitant medication use. Any change in the individual's health status should be recorded on the Medical History page of the CRF (e.g., the subject has been diagnosed with cancer).

Inclusion/exclusion criteria will be reviewed again for the qualified individual.

The following procedures will be performed:

- Heart rate and blood pressure

- Symptomatology: Individuals will be asked "How are you feeling?"

- Best Corrected Visual Acuity

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08:30 hours)

For further evaluation of OAG eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 15 mmHg and < 35 mmHg in both eyes. For further evaluation of OHT eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 22 mmHg and < 35 mmHg in both eyes. [redacted]

Qualified individuals will continue with the measurements of IOP at 10:00 hours and 16:00 hours.

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

Upon return for an unscheduled qualification visit, such individuals' IOP measurements would need to qualify at 08:00, 10:00, and 16:00 hours. Individuals who fail due to IOP being ≥ 35 mmHg in either eye (exclusion criterion) MAY NOT return for additional qualification visits.

Individuals are allowed to leave the Investigator's office between assessments, and eat and drink with no restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.3.2 Visit 3.1 (Day 1, for IOP and safety measurements at 10:00 hours)

Inclusion/exclusion criteria will be reviewed again for the qualified individual. Qualified individuals will be examined. Each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours)

For further evaluation of OAG eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 15 mmHg and < 35 mmHg in the same eye. For further evaluation of OHT eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 22 mmHg and < 35 mmHg in the same eye. [redacted]

Qualified individuals will continue with the qualification visit. Individuals who do NOT meet this requirement may return for up to 2 additional qualification visits within 1 week of failing this qualification visit. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes.

Upon return for an unscheduled qualification visit, such individuals would need to qualify at 08:00, 10:00 and 16:00 hours. Individuals who fail due to IOP being ≥ 35 mmHg in either eye (exclusion criterion) MAY NOT return for additional qualification visits.

Individuals are allowed to leave the Investigator's office between assessments, and eat and drink with no restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.3.3 Visit 3.2 (Day 1, for IOP and safety measurements at 16:00 hours)

Inclusion/exclusion criteria will be reviewed again for the qualified individual. Qualified individuals will be examined. Each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours)

For further evaluation of OAG eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 15 mmHg and < 35 mmHg in the same eye. For further evaluation of OHT eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 22 mmHg and < 35 mmHg in the same eye. [redacted]

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

Upon return for an unscheduled qualification visit, such individuals would need to qualify at 08:00, 10:00 and 16:00 hours. Individuals who fail due to IOP being ≥ 35 mmHg in either eye (exclusion criterion) MAY NOT return for additional qualification visits.

As noted in Section 4.2, subjects must qualify in both eyes based upon IOP and ocular history for a subject who qualifies; the study eye will be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye will be the study eye. In each subject, BOTH eyes will be treated.

At this point, eligible subjects will be randomized. The study medication kit containing 2 bottles will be dispensed to the subject, along with dosing and storage instructions by the site staff.

Subjects will be:

- Instructed to administer their masked medication OU at home between 20:00 - 22:00 hours beginning with the first dose on the evening of this study visit
- Instructed to return to the office with their study medication on Week 1 (Day 8)

For post randomization assessments, a window of ± 2 days for Visit 4 is permitted, and a window of ± 3 days for Visits 5 and 6 is permitted.

7.3.4 Visit 4.0 (Week 1 [Day 8], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use. Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Symptomatology: Individuals will be asked "How are you feeling"?
- Recording of any AEs
- Best Corrected Visual Acuity
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08:30 hours)

After randomization, any new or worsening of symptoms are to be entered as AEs.

Subjects are allowed to leave the Investigator's office between assessments, and eat and drink without restrictions. However, subjects are not to consume alcohol or engage in strenuous exercise.

7.3.5 Visit 4.1 (Week 1 [Day 8], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to10:30 hours)

Subjects are allowed to leave the Investigator's office between assessments, and eat and drink without restrictions. However, subjects are not to consume alcohol or engage in strenuous exercise.

7.3.6 Visit 4.2 (Week 1 [Day 8], for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs.
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours).

Subjects will be:

- Instructed to continue to administer their study medication at home between 20:00 - 22:00 hours (taking the daily evening dose on that day)
- Instructed to return to the office with their used study medication on Week 2 (Day 15)

7.3.7 Visit 5.0 (Week 2 [Day 15], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned regarding any missed doses and any changes in their health or concomitant medication use. Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- Best Corrected Visual Acuity
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08:30 hours)

Any new or worsening of symptoms beyond those collected at baseline are to be entered as AEs.

Subjects are allowed to leave the Investigator's office between assessments, and eat and drink without restrictions. However, subjects are not to consume alcohol or engage in strenuous exercise.

7.3.8 Visit 5.1 (Week 2 [Day 15], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to10:30 hours)

Subjects are allowed to leave the Investigator's office between assessments, and eat and drink without restrictions. However, subjects are not to consume alcohol or engage in strenuous exercise.

7.3.9 Visit 5.2 (Week 2 [Day 15], for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours)

Subjects will be:

- Instructed to continue to administer their masked medication at home between 20:00 - 22:00 hours (taking the daily evening dose on that day)
- Instructed to return to the office with their study medication on Week 4 (Day 29)

7.3.10 Visit 6.0 (Week 4 [Day 29], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use. Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs

- Urine pregnancy test (tests for applicable female subjects of child bearing potential may be performed at any time point throughout Visit 6)

- Blood samples will be taken for clinical chemistry and hematology, and a urine sample will be taken for urinalysis (samples may be taken at any time point throughout Visit 6)

- Best Corrected Visual Acuity

- A non-dilated eye examination will be performed, including IOP and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 07:30 to 08.30 hours)

All used/returned study medication kits will be collected by the site staff and returned to the Sponsor's designee for destruction.

Any new or worsening of symptoms beyond those collected at baseline are to be entered as AEs.

Subjects are allowed to leave the Investigator's office, and eat and drink without restrictions. However, subjects are not to consume alcohol or engage in strenuous exercise.

7.3.11 Visit 6.1 (Week 4 [Day 29], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- Recording of any AEs

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office, and eat and drink without restrictions. However, subjects are not to consume alcohol or engage in strenuous exercise.

7.3.12 Visit 6.2 (Week 4 [Day 29], for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"

- Recording of any AEs

- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured within 30 minutes of the nominal time (i.e., 15:30 to 16:30 hours)

- Dilated ophthalmoscopy examination (including vertical cup-disc ratio)

Subjects will be thanked for their participation, exited from the study, and released to the normal care of their Physician.

7.4 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the specific visits requested in the protocol as 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 adverse events in the CRF.

As noted in Section 6.18.3, every possible effort should be made by Investigators to ensure that non-completing subjects have a final visit that includes all examinations listed for Visit 6.0/Exit (Day 29) as well as dilated ophthalmoscopy.

8. QUALITY CONTROL AND ASSURANCE

The progress of the study will be monitored by on-site, written, remote review, and telephone communications between personnel at the Investigator's site and the Study Monitor. The Investigator will allow the Sponsor or its designee to inspect all CRFs; patient record (source documents); signed consent forms; records of study medication receipt, storage, preparation, and disposition; and regulatory files related to this study.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

All continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and percentages.

Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level. When applicable, two-sided 95% confidence intervals will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001' and p-values greater than 0.9999 presented as '>0.9999'. Differences between netarsudil (0.02% or 0.04%) and placebo will be calculated as netarsudil – placebo.

All study data will be listed by treatment, subject, and time point (as applicable).

For diurnally-adjusted IOP, baseline will refer to the time-relevant measure at Visit 3.0 through 3.2 (e.g., IOP at 08:00 hours at Visit 3.0 will be the baseline for 08:00 hours at Visit 4.0, Visit 5.0, and Visit 6.0; IOP at 10:00 hours at Visit 3.1 will be the baseline for 10:00 hours at Visit 4.1, Visit 5.1, and Visit 6.1; etc.). For all other variables, baseline is defined as the last measurement prior to the first dose of study medication. An additional definition of baseline for conjunctival hyperemia will also be used: baseline (pre-washout) will be defined as the conjunctival hyperemia measure at Visit 1.

The unit of analysis for efficacy will be the study eye. For a subject who qualifies, the study eye will be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye will be the study eye.

Data collected during the observation extension visits may be summarized separately from the data collected during the main portion of the study.

Statistical methods will be more fully described in separate document(s) (i.e., the Statistical Analysis Plan).

9.2 Determination of Sample Size

Assuming a 2-sided test with alpha = 0.05 and a common standard deviation (SD) of 3.5 mmHg at each time point yielding a common SD of 3.0 for the diurnal mean assuming a correlation among time points of 0.60, 49 ITT subjects per arm yields at least 90% power to demonstrate superiority of netarsudil (0.02% or 0.04%) to placebo in mean diurnal study eye IOP (average of 08:00, 10:00, and 16:00 hours) at the Week 4 visit assuming a difference of at least 2.0 mmHg in the mean diurnal IOP. The study will be considered a success and superiority of netarsudil to placebo will be concluded if the two-sided p-value $\leq$ 0.05 at

Week 4. With 60 ITT subjects per arm, each test has 95% power to demonstrate superiority of netarsudil (0.02% or 0.04%) to placebo.

9.3 Analysis Populations

9.3.1 Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects who have received at least 1 dose of study medication. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as randomized.

9.3.2 Per Protocol (PP) Population

The per protocol (PP) population is a subset of the ITT population, 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. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and ITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

9.3.3 Safety Population

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

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, or disease status will be summarized and listed. Medical history, history of ocular surgery and procedures, glaucoma history and washout period (if needed) will also be summarized and listed.

9.5 Primary Efficacy

9.5.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint will be the comparison of netarsudil ophthalmic solution (0.02% or 0.04%) relative to its placebo for mean diurnal IOP within a treatment group at Week 4 (Day29) by Goldmann Applanation Tonometry.

9.5.2 Primary Efficacy Analyses

The primary analysis of the primary endpoint will employ a linear model with mean diurnal IOP at Week 4 as the response, baseline mean diurnal IOP as a covariate, and treatment as a main effect factor, using the ITT population with Monte Carlo Markov Chain multiple imputation techniques used to impute missing data. The least squares mean differences

(netarsudil – placebo) will be presented separately for netarsudil 0.02% and 0.04% as well as 2-sided p-values and 95% confidence intervals (CIs). Inference will be made on the 2-sided p values. Superiority for a concentration (0.02% and 0.04%) will be concluded if the 2-sided p-value, for testing the difference (netarsudil – placebo) to 0, ≤ 0.05 and the point estimate of the difference < 0 at Week 4 for that concentration.

There will be no adjustment for the multiplicity of the 2 active concentrations (0.02% and 0.04%) tested against placebo in this Phase 2 study.

Analyses will be performed primarily on the ITT population using multiple imputation techniques to impute missing data. Sample SAS code to demonstrate the methodology that will be used for data imputation can be found in Appendix 7.

9.6 Secondary Efficacy

9.6.1 Secondary Efficacy Endpoints

- Mean diurnal IOP at Weeks 1 and 2 (Days 8 and 15, respectively)
- Mean change from baseline in mean diurnal IOP at each post-treatment visit
- Mean percent change from baseline in mean diurnal IOP at each post-treatment visit
- Mean IOP at each post-treatment time point
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in mean diurnal IOP levels

Other secondary efficacy analyses may be carried out as described in the study Statistical Analysis Plan. Note that each subject will have one eye designated as the study eye. Only the study eyes will be evaluated for the primary efficacy measure or for selected secondary efficacy measures; however, both eyes will be treated. [redacted]

9.6.2 Secondary Efficacy Analyses

Secondary analyses of the primary efficacy endpoint include repeating the primary analysis strategy using: observed data only, and last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures. These analyses will also be repeated on the PP population to determine robustness of results. Additional imputation techniques may be designated in the formal statistical analysis plan.

Additionally, secondary analyses of the primary endpoint will be completed using individual 2-sample t-tests and 95% t-distribution CIs for each comparison netarsudil (0.02% or 0.04%) versus placebo using the ITT population.

The primary and secondary analyses will also be completed on the secondary endpoints: mean diurnal IOP at Weeks 1 and 2, mean IOP measure at each post-treatment time point and visit (08:00, 10:00, and 16:00 at the Week 1, Week 2, and Week 4 Visits), mean change from baseline in mean diurnal IOP at each post-treatment visit, and mean change from diurnally adjusted baseline IOP at each post-treatment time point and visit. Models adjusting for baseline will only be performed on the mean IOP response variable as inference is identical between this response and the change from baseline IOP response variable in such a model.

Additionally, for the mean IOP values at each time point, mixed model repeated measures will be run with baseline as the covariate; treatment, visit, time point, treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point as the fixed effect factors; and subject as the random effect, repeated measure. An unstructured covariance structure will be used to model the within subject, between visit and time point variances. This allows for different variances and co-variances within and between time points and visits. The treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point interactions allow for a different rate of change in IOP in the different treatment arms among visits and time points. This model will be run including the Week 1, Week 2, and Week 4 visits.

Mean percent change from baseline in mean diurnal IOP and mean percent change from diurnally adjusted baseline IOP at each time point will be analyzed using two-sample t-tests, between netarsudil (0.02% or 0.04%) and placebo, at each time point and visit, including two-sample t-tests and 95% t-distribution confidence intervals on the difference (netarsudil - placebo).

Mean diurnal IOP values will be constructed by averaging the 3 diurnal IOP measurements on each of Week 1, Week 2, and Week 4 visits. Mean diurnal baseline IOP will be constructed as the average of the three Day 1 IOP measurements. Mean change from mean baseline diurnal IOP will be created by taking the average of the 3 time points on each of Week 1, Week 2, and Week 4 visits and subtracting the single mean baseline diurnal IOP measurement.

Sub-group analyses based upon pre-study characteristics such as site, demographics, or pre-study ocular hypotensive medications may be completed to further investigate the efficacy measures.

Analyses of IOP will also include summarizing the number and percentage of study eyes achieving mean diurnal IOP reduction from baseline of ≥ 4 to ≥ 12 mmHg in 2 mmHg increments and percent reduction from baseline of $\geq 5\%$ to $\geq 40\%$ in 5% increments at Week 1, Week 2, and Week 4. Additionally, the number and percentage of study eyes attaining a mean diurnal IOP of ≤ 22 to ≤ 14 mmHg in 1 mmHg increments will be summarized at Week 1, Week 2, and Week 4. Fisher's exact test (2-sided p-values) will be

used to test differences between netarsudil (0.02% or 0.04%) versus placebo for each category at each visit. These analyses will be presented for both the ITT and PP populations with observed data only.

9.7 Safety

9.7.1 Safety Endpoints

- Ocular symptoms/adverse events
- Best corrected visual acuity
- Objective findings of biomicroscopic examinations (i.e., anterior segment examinations including evaluation of cornea, conjunctiva, lids, and lens)
- Dilated ophthalmoscopy, including vertical cup-disc ratio measurements

Other safety assessments will be:

- Systemic safety assessments as measured by heart rate, blood pressure, and clinical laboratory evaluations (including hematology, clinical chemistry, and urinalysis)
- Pregnancy testing (for women of child bearing potential)

9.7.2 Safety Analyses

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and be presented in a data listing. Treatment emergent AEs, those that occur after the first dose of study medication, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Summaries will be presented separately for ocular and non-ocular AEs. These summaries will also be presented for relation to Investigational Product and by severity. Fisher's exact test will be used to test the difference in proportions of subjects with each AE between treatment groups netarsudil (0.02% or 0.04%) vs placebo.

Visual acuity data will be summarized at each time point using both continuous summaries (logMAR), including change from baseline, and discrete summaries, including change from baseline on an ETDRS chart (or equivalent) in the number of lines and the proportion of subjects with a worsening of ≥ 3 lines from baseline.

Slit lamp biomicroscopy and dilated ophthalmoscopy measures will be summarized at each measured time point using discrete summary statistics. Conjunctival hyperemia will also be summarized using continuous summary statistics including change from baseline and change from baseline (pre-washout).

Visual field mean deviation and vertical cup-to-disc ratio will be summarized at each visit and for change from baseline to each visit using continuous summary statistics by treatment group and visit.

Vital signs will be summarized at each visit and for change from baseline to each visit using continuous summary statistics by treatment group and visit.

Clinical laboratory results will be summarized using both continuous summaries, including change from baseline, and discrete summaries, including frequency and percent of subjects with an abnormal value and shift tables from baseline. Additionally, laboratory data will be presented in data listings. A copy of the certification and a table of the normal ranges for the reference laboratory conducting any clinical laboratory tests required by this protocol must be provided.

9.8 Other Assessments or Analyses

Other assessments or analyses will be described in the statistical analysis plan as appropriate.

9.9 Interim Analysis

No interim analysis is planned for this study.

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 is responsible for the safety conduct of this study:

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

This study is to be conducted in accordance with IRB regulations (i.e., US 21CFR Part 56.103) and GCP. The protocol, protocol amendments, informed consent form, and all documents that will be provided to subjects (e.g., subject diary, subject dosing instructions, etc.) will be submitted to the central and/or local IRB(s) for review and approval. This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB prior to initiation of the study. Written IRB approval must adequately identify the protocol and informed consent. 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. In addition to approving the protocol and an Investigator participating in the study, the IRB must also approve the Subject Informed Consent Form, as well as any advertising tools that will be used for the study. Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to the Sponsor prior to the start of subject enrollment into the study.

When the study is completed, the Investigator will provide the governing IRB with a brief final review report.

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 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(s) approving this study, and government regulatory authorities (e.g., 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 CRFs
- 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 CRF entries with subject records), data will be 100% source verified.

10.7 Case Report Forms and Study Records

Study data will be recorded via electronic CRFs. 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 CRF via a secure internet access. Each completed set of CRFs will be reviewed by the Investigator who will then electronically sign and date the CRF 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 CRF; subject charts/source documents; Investigator's Brochure; protocol and 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/IEC 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. 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 10 days, or sooner, if required by the IRB, of becoming aware of any significant protocol deviation. Typically, significant protocol deviations 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

After data have been entered into the study EDC system database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. Where required, the Investigator will be asked for supplementary information through a query. The study EDC system database will be updated by the clinical investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

Once the CRFs are monitored in the EDC system, the data management contract research organization (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 (e.g., range checks, cross checks and other edit checks).

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and US FDA guidelines for the handling and analysis of data for clinical trials. Data will be checked per the data management CRO's SOPs. The database then 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

Aerie Pharmaceuticals, as the Sponsor, has proprietary interest in the study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Aerie Pharmaceuticals personnel, and will be administrated by a steering committee. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Aerie Pharmaceuticals.

11. REFERENCES

11.1 External References

1. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130:429-40.

2. Chen J, Runyan SA, Robinson MR. Novel ocular antihypertensive compounds in clinical trials. Clin Ophthalmol 2011; 5:667-77.

3. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126:498-505.

4. Ferris FL and Bailey I. Standardizing the measurement of visual acuity for clinical research studies. Ophthalmol 1996; 103:181-82.

5. Ferris FL, Kassoff, A, Bresnick GH, et al. New visual acuity charts for clinical research. Am J Ophthalmol 1982; 94:91-6.

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10. Kiel JW, Kopczynski CC. Effect of AR-13324 on episcleral venous pressure in Dutch Belted rabbits. J Ocul Pharmacol Ther 2015; 31(3):146-51.

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glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol 2006; 124:1230-8.

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11.2 Internal References

1. Aerie Pharmaceuticals, Inc., AR-13324 and PG324 Investigator's Brochure (2017).

2. AR-13324-CS101 Clinical Study Report: An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of AR-13324 Ophthalmic Solution 0.02% in Healthy Volunteers (2014).

3. AR-13324-CS102 Clinical Study Report: A double-masked, randomized, paired-comparison, controlled study of the aqueous humor dynamics of AR-13324 Ophthalmic Solution 0.02% in healthy volunteers (2015).

4. AR-13324-CS104: A prospective, double-masked, randomized, multicenter, placebo-controlled, parallel-group study assessing the safety of two concentrations of netarsudil ophthalmic solution in healthy volunteers in the United States.

5. AR-13324-CS201 Clinical Study Report: A Phase 2, double-masked, randomized, placebo-controlled, dose-response study assessing the safety and ocular hypotensive efficacy of three doses of AR-13324 Ophthalmic Solution in patients with elevated intraocular pressure (2012).

6. AR-13324-CS202 Clinical Study Report: A phase 2, double-masked, randomized, multi-center, active-controlled, dose-response parallel-group study comparing the safety and ocular hypotensive efficacy of AR-13324 to latanoprost in patients with elevated intraocular pressure (2013).

7. AR-13324-CS301 Clinical Study Report: A double-masked, randomized, multi-center, active-controlled, parallel, 3-month study assessing the safety and ocular hypotensive efficacy of AR-13324 Ophthalmic Solution, 0.02% compared to timolol maleate ophthalmic solution, 0.5% in patients with elevated intraocular pressure (2016).

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Appendix 1 Schedule of Visits and Procedures

						Post Day 1 Treatment								
Day (D)/Week (W)	Screening	Qual. #1	Qual. #2 (Day 1)			W1 (Day 8±2)			W2 (Day 15±3)			W4 (Day 29±3)		
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0	6.1	6.2
Hour (XY = XY:00)		08	08	10	16	08	10	16	08	10	16	08	10	16
Informed Consent	X													
Inclusion/Exclusion	X	X	X	X	X									
Washout[1]	X													
Demography	X													
Medical/Ophthalmic History	X	X	X											
Concomitant Medications	X	X	X			X			X			X		
HR/BP	X	X	X			X			X			X		
Urine Pregnancy Test[2]	X											X		
Clinical Labs (Chem/Hem/UA)	X[3]											X		
Symptoms/AEs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity	X	X	X			X			X			X		
IOP	X	X[5]	X[5]	X[5]	X[5]	X	X	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy[6]/Ultrasound Pachymetry[7]	G/P													
Visual Field[8]	X													
Ophthalmoscopy (dilated)	X													X
Eye-Drop Instillation Evaluation	X													
Study Medications Dispensed					X									
Study Medications Collected												X[9]		

						Post Day 1 Treatment								
Day (D)/Week (W)	Screening	Qual. #1	Qual. #2 (Day 1)			W1 (Day 8±2)			W2 (Day 15±3)			W4 (Day 29±3)		
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0	6.1	6.2
Hour (XY = XY:00)		08	08	10	16	08	10	16	08	10	16	08	10	16
Study Completed														X

Abbreviations: HR/BP = heart rate/blood pressure; Chem/Hem/UA = Chemistry/Hematology/Urinalysis; AE = adverse event; IOP = Intraocular pressure.

Early Discontinuation: Visit 6.0 procedures are to be completed plus a dilated ophthalmoscopy examination.

Visit Requirements: IOP measurements at all visits are to be made within ±½ hour of the protocol-specified times of 08:00, 10:00, and 16:00 hours with the exception of the Visit 1 (Screening).

[1] Subjects currently using ocular hypotensive medications must undergo a minimum washout period (see Section 5.7.1).

[2] Urine pregnancy test for women of childbearing potential is required.

[3] For subjects who are unable or unwilling to have blood drawn and urine collected for clinical labs at Visit 1 (Screening), the blood and urine sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).

[4] Ocular symptoms: Subjects will be queried at each visit "How are you feeling?" and treatment emergent AEs beginning at Visit 4 will be documented on the AE form. Additional symptoms reported after screening and before randomization will be documented on the medical history form. Adverse events will be recorded for every study visit (i.e., at 08:00, 10:00, and 16:00 hours) as needed.

[5] Individuals returning at an Unscheduled Visit within 1 week to re-attempt IOP qualification are required to only re-measure IOP in both eyes.

[6] Gonioscopy evaluation up to 3 months prior to randomization is acceptable.

[7] Ultrasound pachymetry within 1 week prior to screening is acceptable.

[8] Entry visual field evaluation up to 3 months prior to randomization is acceptable. Visual field collection must meet the requirement for automated threshold visual field assessment (e.g., 30-2 or 24-2 Humphrey) and reliability.

[9] Collect kit(s) dispensed during the Day 1 visit.

Appendix 2 Procedures

Procedures: Best Corrected Visual Acuity

Best corrected visual acuity (BCVA) is taken at all visits as a measure of ocular function. BCVA will be measured at screening and frequently throughout the study.

Procedure: Distance visual acuity must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) or equivalent chart. Visual acuity testing should precede intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the anterior segment.

Distance visual acuity will be measured with best correction.

The visual acuity chart may be either retro-illuminated ("back-lit"), or reflectance illuminated. If the latter is chosen, then the illumination must be checked at regular intervals to be consistent with ETDRS guidelines. Standard charts for a distance from subject to chart of 10 feet to 20 feet must be used. Ideally, the subject should be seated. The right eye should be tested first. Sites are directed to refer to the instructions on the commercial ETDRS charts. If there is any question, contact the Sponsor's monitor.

The subject should attempt to read each letter, line by line, left to right, beginning with line 1 at the top of the chart (20/200 line). The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subjects should be asked to read slowly, about 1 letter per second, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, he/she should be encouraged to guess. If the subject identified 2 letters (e.g., A or B), he/she should be asked to choose 1 letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made despite encouragement to read or guess, the examiner should stop the testing for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last letter may be the only one read correctly. The number of letters missed or read incorrectly should be noted. Repeat with left eye.

In order to provide standardized and well-controlled assessment of visual acuity during the study, all visual acuity assessments for a subject must be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) during the entire study.

The number of letters missed is multiplied by 0.02 and added to the baseline value to determine the logMAR visual acuity. Baseline is defined as the last line for which the subject reads at least 1 letter.

logMAR units BCVA = Baseline value + (n x 0.02)

If refraction was used at Visit 1 (Screening), at Visit 2, or at Visit 3/Day 1 (Baseline), then this refraction should be used in the phoropter or trial frame for all subsequent examinations. A repeated refraction is not required at these subsequent examinations.

A priori, a decrease of 3 lines in visual acuity in either eye is considered clinically significant.

Procedures: Visual Field Examination

Visual fields must be automated threshold visual fields (e.g., 30-2 or 24-2 Humphrey) performed in both eyes within 3 months prior to randomization. C-24 SITA Standard is preferred; SITA fast is also allowed. Visual fields must be reliable, defined as those with: a) fixation losses less than or equal to 33%, b) false positives less than or equal to 33%, and c) false negatives less than or equal to 33%. Visual fields fixation losses should not be rounded up to the next whole number value. **The gaze track and blind spot should be turned on for all visual fields assessments in order to calculate the fixation losses.**

Visual fields are required to be performed at study entry with a non-dilated pupil unless, in the opinion of the Investigator, the pupil is so miotic that dilation is required (e.g., < 3 mm).

The complete visual field reports will be provided to the Sponsor with subject names removed.

Procedures: Measurement of Intraocular Pressure (IOP)

Two consecutive IOP measurements of each eye must be obtained. If the 2 measurements differ by more than 2 mmHg, a third measurement must be obtained. Intraocular pressure will be analyzed as the mean of 2 measurements or as the median of 3 measurements (Sherwood 2006).

Local anesthetic will also be applied in order to facilitate IOP measurements with the Goldmann Applanation Tonometer. Intraocular pressure should be measured by qualified individuals using a calibrated Goldmann applanation tonometer. Tonometer calibration on at least a monthly basis must be documented. Each Goldmann tonometry value is read as an integer. When calculating the mean or median, it is possible to have a fractional value; any non-integral mean or median IOP number will be reported to one decimal place. [redacted]

Procedures: Biomicroscopy

The subject will be seated while being examined.

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice.

The clinician will examine and grade the eyelids of both eyes for evidence of erythema and/or edema. Observations will be documented on the appropriate CRF. The clinician will examine the conjunctiva, cornea, anterior chamber, iris, pupil, and lens of the eye with the aid of a slit lamp, which is a table-mounted binocular microscope, and report their gradings for these tissues. Fluorescein dye will be instilled into the ocular cul-de-sac to facilitate this examination. The Sponsor recommends that the same examiner should conduct all biomicroscopy examinations at each time point and at each visit for a given subject.

Biomicroscopic grading will be done as follows:

LID

Erythema

None (0)=	Normal, without any redness, or less than mild
Mild (+1)=	A low grade flushed reddish color
Moderate (+2)=	Diffused redness encompassing the entire lid margin
Severe (+3)=	Deep diffused reddish color of lid margins and superior or inferior eyelid

Edema

None (0)=	Normal, no swelling of the lid tissue, or less than mild
Mild (+1)=	Slight diffuse swelling above normal
Moderate (+2)=	General swelling
Severe (+3)=	Extensive swelling of the eyelid(s), with or without eversion of upper and/or lower lids

CONJUNCTIVA

Hyperemia

None (0)=	Normal. Appears white with a small number of conjunctival blood vessels easily observed.
Mild (+1)=	Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva;
Moderate (+2)=	Bright, scarlet red color of the bulbar and palpebral conjunctiva
Severe (+3)=	“Beefy Red” with petechiae --- Dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage

Edema

None (0)=	Normal, no swelling of the conjunctiva or less than mild
Mild (+1)=	Slight diffuse or regional swelling of the conjunctiva
Moderate (+2)=	General swelling of the conjunctiva
Severe (+3)=	Extensive swelling of the conjunctiva

CORNEA

Edema

None (0)=	Transparent and clear or less than mild
Mild (+1) =	Dull glassy appearance
Moderate (+2)=	Dull glassy appearance of epithelium with large number of vacuoles
Severe (+3) =	Stromal edema, localized or diffuse, with stromal striae

Staining

None (0)=	No fluorescein staining of epithelium, OR less than mild
Mild (+1) =	Slight punctate fluorescein staining
Moderate (+2)=	Regionally dense coalescent fluorescein staining
Severe (+3) =	Marked fluorescein staining with immediate stromal leakage as a result of epithelial loss

ANTERIOR CHAMBER

Cells

None (0)=	No cells seen or less than mild
Mild (+ 1) =	+ cells (1-5 cells)
Moderate (+2) =	++ cells (6-15 cells)
Severe (+3) =	+++ cells (> 15 cells, no hypopyon)
Hypopyon (+4)=	++++ cells (> 15 cells plus hypopyon formation [indicate size of hypopyon])

Flare

None (0)=	No Tyndall effect or less than mild
Mild (+1) =	Tyndall beam in the anterior chamber has a mild intensity
Moderate (+2) =	Tyndall beam in the anterior chamber is of strong intensity
Severe (+3) =	Tyndall beam is very intense. The aqueous has a white, milky appearance

LENS PATHOLOGY

Lens status

Phakic
Pseudophakic
Aphakic

Lens Opacity (Phakic only)

None (0)=	None present or less than mild
Mild (+ 1)=	Subtle
Moderate (+2)=	Moderate
Severe (+3)=	Dense

Procedures: Dilated Ophthalmoscopy

The Sponsor recommends that the same masked examiner should conduct all ophthalmoscopy exams for a given subject.

RETINA, VITREOUS, MACULA, CHOROID, OPTIC NERVE

0= Normal
1= Abnormal

CUP-DISC RATIO (Vertical)

Score from 0.1 to 1.0 in 0.1 increments

A priori, a change of 0.2 units in either eye is considered clinically significant.

Procedures: Pachymetry - Central Corneal Thickness

Central corneal thickness will be measured by ultrasound pachymetry in both eyes (mean of 2 readings per eye). The mean value will be used for enrollment criteria.

For individuals with mean central corneal thickness greater than 620 μm, they may return either the same day, or within 7 days for another pachymetry measurement. If the mean of 2 readings on that second pachymetry is ≤ 620 μm, then the individual may be considered for the study.

Procedures: Gonioscopy

The purpose of this examination is to confirm that the iridocorneal angle is open, and that the subject does not have narrow angle glaucoma, which is an exclusion criteria for study participation. Gonioscopy may be performed up to 3 months prior to randomization. Gonioscopy will be performed at the slit lamp, bilaterally, using a goniolens and grading will be by the Shaffer grading scale (Stamper 2009).

Procedures: Symptomatology

Subjects will be queried “How are you feeling?” and any treatment emergent adverse events will be documented on the adverse event form.

Procedures: Heart Rate

Heart rate will be measured after the subject has been seated quietly for at least 5 minutes. Pulse will be detected at the wrist, and will be counted for 30 seconds, and multiplied by 2. If an electronic measurement device is used, it must be documented.

Procedures: Blood Pressure

Blood pressure will be measured after heart rate (and thus the subject will already be in a resting state). Blood pressure will be measured using a sphygmomanometer with appropriate size cuff and a stethoscope or with a measurement device.

Procedures: Urine Pregnancy Test

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

The Sponsor will provide urine pregnancy tests to the sites. Expiration dates on the pregnancy tests will be reviewed and confirmed by the site prior to use.

If a female becomes pregnant during the study, the Investigator should notify the Sponsor immediately after the pregnancy is confirmed and the subject will be exited from the study. The Investigator should follow the progress of the pregnancy until the fetus is carried to term.

Procedures: Clinical Laboratories

Central laboratories should be used for clinical chemistries as mandated by the protocol. A copy of the certification for the reference laboratory conducting any clinical laboratory tests required by this protocol will be provided. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number and visit date. Details for the preparation and shipment of samples and reference ranges will be provided in the laboratory manual.

A chemistry panel, complete blood count (hematology and differential), and urinalysis will be performed as shown below. Note that fasting is NOT required and specific values may be out of the typical fasting range.

- **Clinical Chemistry:**
    - A/G ratio (albumin/globulin)
    - Alanine aminotransferase (ALT)
    - Albumin
    - Alkaline phosphatase
    - Aspartate aminotransferase (AST)
    - Blood urea nitrogen (BUN)

- BUN/Creatinine ratio
- Calcium
- Carbon Dioxide
- Chloride
- Creatinine
- Globulin (calculation from total protein and albumin)
- Glucose
- Potassium (K)
- Sodium (Na)
- Total Bilirubin
- Total Protein
- Triglycerides

- **Hematology:**
  - White blood cells
    - Differential Including:
      - Absolute and Percent Neutrophil Count
      - Absolute and Percent Lymphocyte Count
      - Absolute and Percent Monocyte Count
      - Absolute and Percent Eosinophil Count
      - Absolute and Percent Basophil Count
  - Platelets:
    - Mean Platelet Volume
    - Platelet count
  - Red blood cells

  - Hemoglobin
  - Hemoglobin A1c
  - Hematocrit
  - Mean corpuscular volume
  - Mean corpuscular hemoglobin
  - Mean corpuscular hemoglobin concentration
  - Red Cell Distribution Width

- **Urinalysis**

Appendix 3 Sponsor's Obligations

Aerie Pharmaceuticals, Inc. is committed to:

A. Complying with the local health authority regulations for the conduct of clinical research studies.

B. 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.

C. 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 Sponsor is responsible for notifying the regulatory authority(ies) immediately (see Section 6.9, Adverse Events Assessments).

D. 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).

E. 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.

F. Providing study medications suitably masked/blinded, coded, and packaged for use with subjects entered into the study.

G. Providing statistical and report writing resources to complete appropriate reporting of study results.

H. Ensuring equity considerations among all Investigators in multicenter studies, including all matters of publications and meeting presentations, etc. (where applicable).

I. 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:

A. 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 6.9, Adverse Events Assessments). The Investigator must also notify the Sponsor Representative and the IRB to which he/she is responsible.

B. 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.

C. 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).

D. Obtain and submit to the Sponsor a copy of his/her IRB approval of the protocol prior to initiating the study.

E. Obtain signed informed consent from each subject or his/her legal guardian prior to acceptance of the subject into the study.

F. 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 1 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.

G. Accurately record, at the Investigator's site, all required data on each subject's CRF.

H. 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.

I. Assure that IP 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.

J. Allow a representative of the Sponsor and/or representatives of health regulatory agencies to inspect all CRFs and corresponding portions of each study subject's 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 onsite 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 CRFs, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.

K. Provide the governing IRB with a brief (i.e., 1 to 3 pages) Investigator's summary within 90 working days of the study completion.

L. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study.

M. 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 the 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)

1. 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.

2. The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. 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.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. 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.

6. 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 patient.

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

1. 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.

2. The subjects should be volunteers - either healthy person or subjects for whom the experimental design is not related to the patient's illness.

3. 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.

4. In research on man, the interest of science and society should never take precedence over consideration related to the well-being of the subject.

Appendix 6 Study Monitoring

1. Member(s) of the Sponsor or designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's patient population, facilities, and equipment, and to familiarize the Investigator with the protocol.

2. A member of the Sponsor or designee will meet with the Investigator after several of the subjects have initiated the study in order to ensure that the subjects are being properly selected, that adequate supplies for the study have been provided, and that the assignment of medication is properly recorded. In addition, the Study Monitor will verify that the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Instigator's regulatory documents, source document, Informed Consent Forms, and Case Report Forms of study subjects.

3. A member of the Sponsor or designee will meet with the Investigator when all subjects have completed the Final Visit of the study, in order to collect the Case Report Forms, unused study medications, and unused supplies and materials.

4. Interim monitoring visits and telephone consultations will be done by the Study Monitor, as necessary, to ensure the proper progression and document of the study.

Appendix 7 Sample SAS Code

The following SAS code will be used for multiple imputations using the Monte-Carlo Markov Chain method, where a separate model will be fit for each time point at each visit.

```
proc mi data = indata seed = 6876 out = outdata1;

mcmc initial = em;

var trt01pn baseline IOP;

run;
```

where

- *indata* is the name of the input dataset
- *outdata1* is the name of the output dataset
- *trt01pn* is the name of the treatment group variable in numeric format
- *baseline* captures the baseline IOP for the given time point
- *IOP* is the name of the IOP measure.

Thirty complete data sets will be generated from the above code. Each complete data set will be used to analyze this primary efficacy endpoint separately using analysis of variance. Then, the SAS procedure MIANALYZE will be used to analyze the results from the 30 complete data sets to generate a combined inference. The following SAS code will be used:

```
ods output diffs = outdata2;

proc mixed data= outdata1;

    by _IMPUTATION_;

    class trt01pn;

    model IOP = trt01pn baseline;

    lsmeans trt01pn / cl pdiff;

run;
```

proc sort data= *outdata2*;

by *trt01pn _trt01pn*;

run;

ods output ParameterEstimates = *outdata3*;

proc mianalyze data= *outdata2* alpha = 0.05;

by *trt01pn _trt01pn*;

class *trt01pn _trt01pn*;

modeleffects estimate;

stderr;

run;

where

- *outdata1* is the name of the input dataset from Proc MI
- *_IMPUTATION_* is the imputation number
- *trt01pn* is the name of the treatment group variable in numeric format
- *IOP* is the name of the IOP measure
- *baseline* captures the baseline IOP for the given time point
- *outdata2* is the name of the output dataset that contains the statistical results of the difference between treatment groups
- *outdata3* is the name of the output dataset that contains summary and inferential statistics.