# Efficacy and Safety Study of Netarsudil 0.02% Ophthalmic Solution Compared to Ripasudil Hydrochloride Hydrate 0.4% Ophthalmic Solution in Japanese Subjects With Primary Open Angle Glaucoma or Ocular Hypertension

NCT04620135

Amendment 1 (Rev 1) dated 11 January 2021

# Clinical Study Protocol

| | |
|---|---|
| **Study Title:** | A single-masked, randomized, multi-center, parallel-group, 4-week study evaluating the efficacy and safety of once daily netarsudil ophthalmic solution 0.02% compared to twice daily ripasudil hydrochloride hydrate ophthalmic solution 0.4% in Japanese subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT) |
| **Study Number:** | AR-13324-CS305 |
| **Study Phase:** | Phase 3 |
| **Product Name:** | Netarsudil Ophthalmic Solution 0.02% |
| **Indication:** | Reduction of elevated intraocular pressure (IOP) in subjects with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) |
| **Investigators:** | Multicenter |
| **Sponsor:** | Aerie Pharmaceuticals Ireland Limited |
| **Sponsor Contact:** | [redacted] |
| **Medical Monitor:** | [redacted] |
| **ClinicalTrials.gov Identifier:** | NCT04620135 |

| | Date |
|---|---|
| **Original Protocol (Rev 0):** | 29 July 2020 |
| **Amendment 1 (Rev 1):** | 11 January 2021 |

## Confidentiality Statement

# CLINICAL PROTOCOL APPROVAL FORM

**Protocol Title: A single-masked, randomized, multi-center, parallel-group, 4-week study evaluating the efficacy and safety of once daily netarsudil ophthalmic solution 0.02% compared to twice daily ripasudil hydrochloride hydrate ophthalmic solution 0.4% in Japanese subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT)**

**Study No: AR-13324-CS305**

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**Protocol Version No: Rev 1**

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| Role | Contact information |
|---|---|
| **Clinical Operations** | [redacted]<br>DocuSigned by:<br>[redacted]<br>Signing Reason: I approve this document<br>Signing Time: 11-Jan-2021 \| 23:47 EST<br>5434888FA63D46E5B41CAB2FF0FF2638<br>Signature Date |
| **Aerie Management and Sponsor Safety Officer** | [redacted]<br>DocuSigned by:<br>[redacted]<br>Signing Reason: I approve this document<br>Signing Time: 11-Jan-2021 \| 18:31 EST<br>D31A663F730F4A808E6630BC6595E314<br>Signature Date |

**Medical Monitor**

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**Biostatistics and Data Management**

[redacted]

# SYNOPSIS

**Sponsor:** Aerie Pharmaceuticals Ireland Ltd.

**Name of Finished Product:** Netarsudil ophthalmic solution 0.02%

**Name of Active Ingredients:** Netarsudil

**Study Title:**
A single-masked, randomized, multi-center, parallel-group, 4-week study evaluating the efficacy and safety of once daily netarsudil ophthalmic solution 0.02% compared to twice daily ripasudil hydrochloride hydrate ophthalmic solution 0.4% in Japanese subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT)

**Study Number:** AR-13324-CS305

**Study Phase:** Phase 3

**Primary Objective(s):**
The objective of this study is to evaluate the ocular hypotensive efficacy and safety of netarsudil ophthalmic solution 0.02% QD compared to the active comparator, ripasudil hydrochloride hydrate ophthalmic solution 0.4% BID, over a 4-week period (superiority study).

**Study Design:**
This will be a prospective, single-masked, randomized, multi-center, parallel-group, 4-week study evaluating the efficacy and safety of once daily (QD) netarsudil ophthalmic solution 0.02% compared to twice daily (BID) ripasudil hydrochloride hydrate ophthalmic solution 0.4% in Japanese subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT) in Japan.

Netarsudil ophthalmic solution, 0.02% will be dosed QD (21:00) while ripasudil hydrochloride hydrate ophthalmic solution, 0.4% will be dosed BID (9:00/21:00). In order to be adequately masked, subjects dosing with netarsudil ophthalmic solution 0.02% (21:00) also will dose with netarsudil ophthalmic solution, Vehicle QD (9:00).

Subjects eligible to be enrolled in this study will be subjects with diagnosis of either POAG or OHT. Approximately 240 subjects will be enrolled in this study. Subjects who agree to participate in this study and are enrolled will attend a total of up to 6 study visits: 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 will be required to washout of their pre-study ocular hypotensive medication for a prescribed period (i.e., 5 days to 6 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 intraocular pressure (IOP) measurements at the Screening Visit and Qualification Visits #1 and #2 and undergo additional testing at Qualification Visit #2. If deemed eligible, subjects will be enrolled at Qualification Visit #2 and assigned to either the netarsudil group or ripasudil group in a 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 study drug in both eyes BID in the morning (9:00 ± 1 hour) and in the evening (21:00 ± 1hour) 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 pre-dose, 2 hours and 7 hours post-dose of the dose in the morning. 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.

**Study Population:**
A total of approximately 240 subjects will be enrolled in this study at approximately 28 clinical sites, comprising a total of 120 subjects per treatment arm for each of two treatment arms. Subjects will be at least 20 years of age with diagnosed POAG or OHT, each of whom meets all inclusion criteria and none of the exclusion criteria.

**Inclusion Criteria:**

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

1. 20 years of age or older
2. Diagnosis of POAG or OHT in both eyes (POAG in one eye and OHT in the fellow eye is acceptable)
3. Medicated intraocular pressure (IOP) ≥ 14 mmHg in at least one eye and < 30 mmHg in both eyes at screening visit (this also applies to treatment naive subjects)
4. For POAG eyes, unmedicated (post washout) IOP ≥ 15 mmHg and < 35 mmHg in the study eye at 2 qualification visits (09:00 hour), 2-7 days apart. At second qualification visit IOP ≥ 15 mmHg and < 35 mmHg at 11:00 and 16:00 hours (in the same eye).
5. For OHT eyes, unmedicated (post washout) IOP ≥ 22 mmHg and < 35 mmHg in the study eye at 2 qualification visits (09:00 hour), 2-7 days apart. At second qualification visit IOP ≥ 22 mmHg and < 35 mmHg at 11:00 and 16:00 hours (in the same eye).
6. Best-corrected visual acuity (BCVA) +0.7 log MAR or better (20/100 Snellen or better or 0.20 or better in decimal unit) in each eye
7. Willingness and ability 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 a maximum of 8 weeks is not judged safe as it would put the subject at risk for further vision loss
2. Retinal diseases that may progress during the study period (e.g., Macular edema, retinal detachment, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, pathological myopia)
3. 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
4. Ocular hyperemia score of moderate (+ 2) or severe (+3) 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. Any corneal disease or condition in either eye that in the Investigator's opinion, may confound assessment of the cornea
10. Current evidence of corneal deposits or cornea verticillata in either eye
11. Planned use of any prohibited concomitant medications in either eye during the study
12. Mean central corneal thickness greater than 620 μm in either eye at screening
13. Any abnormality preventing reliable Goldmann applanation tonometry of either eye (e.g., keratoconus)
14. Known hypersensitivity to any component of netarsudil ophthalmic solution 0.02%, ripasudil hydrochloride hydrate ophthalmic solution 0.4%, or to topical anesthetic.
15. Cannot demonstrate proper delivery of the eye drop, or in the Investigator or Co-investigator's opinion, unable to deliver the eye drop consistently

**Systemic:**

16. Clinically significant systemic disease which might interfere with the study or place the subject at risk
17. Participation in any investigational study within 30 days prior to screening
18. 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
19. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable birth control includes: condoms plus intrauterine devices or condoms plus oral hormonal contraceptives, double barrier methods (e.g., condoms with spermicidal gel plus diaphragms). Birth control must be continued for at least 30 days after the last dose of the study drug. 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 drug, Dose, and Mode of Administration:**

- Netarsudil ophthalmic solution Vehicle, 1 drop QD (9:00), in both eyes (OU)
- Netarsudil ophthalmic solution 0.02%, 1 drop QD (21:00), OU
- Ripasudil hydrochloride hydrate ophthalmic solution 0.4%, 1 drop BID (9:00/21:00), OU

**Duration of Treatment:**

Dosing will continue daily for approximately 28 days continuously.

**Efficacy Assessments:**

The primary efficacy endpoint will be mean diurnal IOP at Week 4 (Day 29) for netarsudil ophthalmic solution 0.02% relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% by Goldmann Applanation Tonometry. Superiority of netarsudil ophthalmic solution 0.02% QD to ripasudil hydrochloride hydrate ophthalmic solution 0.4% BID in the study eye is tested.

Secondary efficacy endpoints will be comparison of netarsudil ophthalmic solution 0.02% QD relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% BID 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:**

Primary safety assessments:

- Ophthalmic and systemic adverse events (AEs)
- BCVA
- 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

Additional safety assessments:

- Systemic safety assessments as measured by heart rate and blood pressure
- Pregnancy testing (for women of childbearing potential)

**Statistical Methods:**

Summaries will be presented by treatment, visit, and time point (as applicable). Continuous and ordinal study assessments will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Discrete study assessments will be summarized using frequency counts and percentages.

Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level.

Hypotheses:

H0: The difference in mean diurnal IOP in study eyes treated with netarsudil QD versus study eyes treated with ripasudil BID (netarsudil QD – ripasudil BID) at Week 4 = 0.

H1: The difference in mean diurnal IOP in study eyes treated with netarsudil QD versus study eyes treated with ripasudil BID (netarsudil QD – ripasudil BID) at Week 4 ≠ 0.

Sample Size:

Ninety three (93) subjects (study eyes) per treatment group are required to have 90% power (1-β) to reject H0 in favor of H1 at a two-sided significance level of 5%, assuming that a difference of the change from baseline in mean diurnal IOP between netarsudil and ripasudil (netarsudil QD – ripasudil BID) in the present study is -1.1 mmHg with a common standard deviation of 2.3. The target sample size is set to 120 per treatment group to allow for withdrawals and dropouts. Note that change from baseline values from historic studies are being used as estimates from which to calculate sample size for a non-change from baseline primary endpoint due to the change from baseline estimates for standard deviation better reflecting the standard deviation obtained from the primary analysis strategy within this study.

Primary Efficacy Population and Analysis:

The intent-to-treat (ITT) population will include all randomized subjects who have received at least one 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.

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 as defined in the intercurrent event strategy within the body of the protocol. The least squares mean difference (netarsudil QD – ripasudil BID) will be presented as well as the 2-sided p-value and 95% confidence interval (CI). Inference will be made on the 2-sided p value. Superiority of netarsudil QD over ripasudil BID will be concluded if the 2-sided p-value, for testing the difference (netarsudil QD – ripasudil BID) to 0, ≤ 0.05 and the point estimate of the difference < 0.

**Date of Original Approved Protocol (Rev 0):** 29 July 2020

**Date of Most Recent Protocol Amendment (Rev 1):** 11 January 2021

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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|---|---|
| AE | Adverse Event |
| ALT | Argon Laser Trabeculoplasty |
| AM | Morning |
| BCVA | Best-Corrected Visual Acuity |
| BID | Twice daily |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CTN | Clinical Trial Notification |
| EDC | Electronic Data Capture |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| hCG | Human Chorionic Gonadotropin |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| 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 |
| LS | Least Squares |
| MAA | Marketing Authorisation Application |
| mmHg | Millimeters of Mercury |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHLW | Ministry of Health, Labor and Welfare |
| MOPs | Manual of Procedures |
| NDA | New Drug Application |
| OHT | Ocular Hypertension |
| OTC | Over-the-Counter |
| OU | Both Eyes |
| PM | Evening |
| PGA | Prostaglandin |

| | |
|---|---|
| PLD | Phospholipidosis |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| POAG | Primary Open-Angle Glaucoma |
| 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 |
| SITA | Swedish Interactive Thresholding Algorithm |
| SLT | Selective Laser Trabeculoplasty |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SSAR | Suspected Serious Adverse Reaction |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment Emergent Adverse Event |
| 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 (IOP) (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 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 (Chen 2011; Kopczynski 2014). Netarsudil mesylate (AR-13324) is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. (Aerie) 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, AR-13324-CS304, AR-13324-CS205 and AR-13324-CS208), and reduces IOP potentially through several mechanisms: increasing trabecular outflow (Clinical Study Report AR-13324-CS102; Clinical Study Report AR-13324-CS206; 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; Clinical Study Report AR-13324-CS206; Kiel 2015). Aerie filed a New Drug Application for once-daily netarsudil 0.02% on February 28, 2017 (NDA 208254 for Rhopressa®) which was approved by US FDA on December 18, 2017. A Marketing Authorization Application (MAA) was submitted on September 10, 2018 in the EU under the trade name of Rhokiinsa®, which was approved by the European Commission on November 19, 2019.

Cornea verticillata, a whorl-like pattern of deposits typically localized to the basal corneal epithelium (Mantyjarvi 1998; Hollander 2004) have been reported in Aerie's completed Phase 3 studies (AR-13324-CS301, AR-13324-CS302, AR-13324-CS303, and AR-13324-CS304). A variety of cationic, amphiphilic drugs are known to induce cornea verticillata, which arise due to the accumulation of phospholipids within corneal epithelial cells through a process called phospholipidosis (PLD). Amiodarone, an antiarrhythmic agent, is the most common cause of cornea verticillata, followed by chloroquine, hydroxychloroquine, indomethacin, and phenothiazines (Raizman 2017). It is unusual for

these deposits to result in reduction of visual acuity or ocular symptoms, and the deposits typically resolve with discontinuation of the drug (Mantyjarvi 1998). Corneal changes due to amiodarone have been studied over a long period of time and are well characterized; it is of note that no routine monitoring, or specific treatment, or precautions are recommended for amiodarone-induced cornea verticillata (Ingram 1982, Siddoway 2003).

The corneal verticillata associated with the use of netarsudil were first detected between 2-13 weeks, dose dependent, observed in 16.7% (76/454) of netarsudil QD subjects and 25.3% (64/253) of netarsudil BID subjects. Aerie carried out an observational cohort study (AR-13324-OBS01) to follow up the cases of cornea verticillata and demonstrated that cornea verticillata did not have any clinically meaningful impact on visual function and appeared to resolve after dosing was discontinued.

For the development in Japan, two Phase 1 studies (AR-13324-CS103; study CS103 and AR-13324-CS104; study CS104) that enrolled Japanese-American subjects within the second generation were conducted and completed in the United States to evaluate the tolerability and safety of netarsudil 0.02%. In study CS103, pharmacokinetics of netarsudil was also evaluated. The results of those two Phase 1 studies demonstrated that the netarsudil 0.02% formulations were safe and generally well tolerated by the healthy volunteer subjects of Japanese ethnicity within the 2nd generation who participated in this study.

Recently, a Phase 2 study to assess the efficacy and safety of netarsudil ophthalmic solution (0.01%, 0.02% and 0.04%) compared to placebo over a 28-day period in Japanese subjects with POAG or OHT was completed (AR-13324-CS208). Netarsudil ophthalmic solution 0.01%, 0.02% and 0.04% demonstrated clinically relevant efficacy and met primary endpoint of superiority to placebo in mean diurnal IOP at Week 4 in Japanese subjects. Baseline-adjusted least squares (LS) mean diurnal IOP at Week 4 (mean value of IOP at 9:00, 11:00, and 16:00) was 18.94 mmHg in the placebo group, while it was 16.53, 15.82 and 16.06 mmHg in the netarsudil 0.01%, 0.02% and 0.04% groups, respectively. The mean difference (netarsudil – placebo) (adjusted LS mean [95% confidence interval]) was -2.41 (-3.15, -1.67), -3.12 (-3.87, -2.38) and -2.88 (-3.66, -2.10) mmHg in the netarsudil 0.01%, 0.02% and 0.04% groups, respectively, in which a difference between the placebo group and any of the netarsudil 0.01%, 0.02% and 0.04% groups met the pre-defined statistically significant level (p-value is <0.05 and the point estimate of the LS mean difference < 0). The ocular hypotensive efficacy of netarsudil 0.01% was slightly less than netarsudil 0.02% and 0.04% at Week 4.

In terms of safety, netarsudil ophthalmic solution 0.01%, 0.02% and 0.04% administered QD were safe and generally well tolerated in Japanese subjects with POAG or OHT based upon a review of adverse events (AEs) and an assessment of ocular parameters, vital signs, and clinical laboratory findings. Number of subjects with at least one treatment emergent adverse event (TEAE) was 21 (38.2%), 27 (50.0%), and 36 (70.6%) in the netarsudil 0.01%, 0.02%, and 0.04% groups, respectively, representing increased incidence with higher dose of netarsudil. The most frequent ocular TEAEs were conjunctival hyperemia which was scored as mild in the majority of the subjects.

In conclusion, netarsudil 0.02% was deemed to provide optimum efficacy and safety based on the results of the study, and 0.02% was determined to be the clinically optimum concentration of netarsudil for Japanese population.

The present study is a Phase 3 study to evaluate the ocular hypotensive efficacy and safety of netarsudil ophthalmic solution 0.02% QD compared to the active comparator, ripasudil hydrochloride hydrate ophthalmic solution 0.4% BID, over a 4-week period (superiority study).

## 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/biodistribution 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 and phototoxicity studies.

### Clinical

The clinical development of netarsudil ophthalmic solution for Japan includes pharmacokinetics, tolerability, and dose-response investigations. The assessment of the ocular and systemic safety of netarsudil ophthalmic solution 0.02% for Japanese ethnicity in two Phase 1 clinical studies (Clinical Study Reports AR-13324-CS103 and AR-13324-CS104) have been completed. Results from a previous Phase 2 study (Clinical Study Report AR-13324-CS208) investigating a range of netarsudil concentrations (0.01%, 0.02%, and 0.04%) in Japanese patients with POAG or OHT were used to select the appropriate concentration of netarsudil ophthalmic solution to be tested in the present study (0.02%).

Four overseas Phase 3 clinical studies (Clinical Study Reports AR-13324-CS301, AR-13324-CS302, AR-13324-CS303, and AR-13324-CS304) evaluating the safety and efficacy of 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

Netarsudil ophthalmic solution 0.02% was approved in the US on December 18, 2017 and in the EU and the UK on November 19, 2019 under the trade name of Rhopressa® and

Rhokiinsa®, respectively. In the US Phase 3 studies, AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304, netarsudil ophthalmic solution 0.02% QD demonstrated non-inferiority to timolol 0.5% BID in subjects with POAG or OHT, and it was safe and generally well tolerated. The most common ocular adverse reaction observed in controlled clinical studies with netarsudil ophthalmic solution 0.02% QD was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: cornea verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients (Rhopressa® PI).

AR-13324-CS208, a Phase 2 study in Japan, netarsudil ophthalmic solution 0.01%, 0.02% and 0.04% demonstrated clinically relevant efficacy and met primary endpoint of superiority to placebo in mean diurnal IOP at Week 4 in the primary efficacy population. Netarsudil ophthalmic solution 0.01%, 0.02% and 0.04% administered QD were safe and generally well tolerated in Japanese subjects with POAG or OHT based upon a review of AEs and an assessment of ocular parameters, vital signs, and clinical laboratory findings.

- Number of subjects with ≥1 TEAE was 21 (38.2%), 27 (50.0%), and 36 (70.6%) in the netarsudil 0.01%, 0.02%, and 0.04% groups, respectively, representing increased incidence with higher dose of netarsudil.

- Most (95.2%) TEAEs (ocular and non-ocular) in the netarsudil groups were reported as being of mild severity.

- The most frequent ocular TEAE was conjunctival hyperemia which was scored as mild in the majority of the subjects.

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 POAG or 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

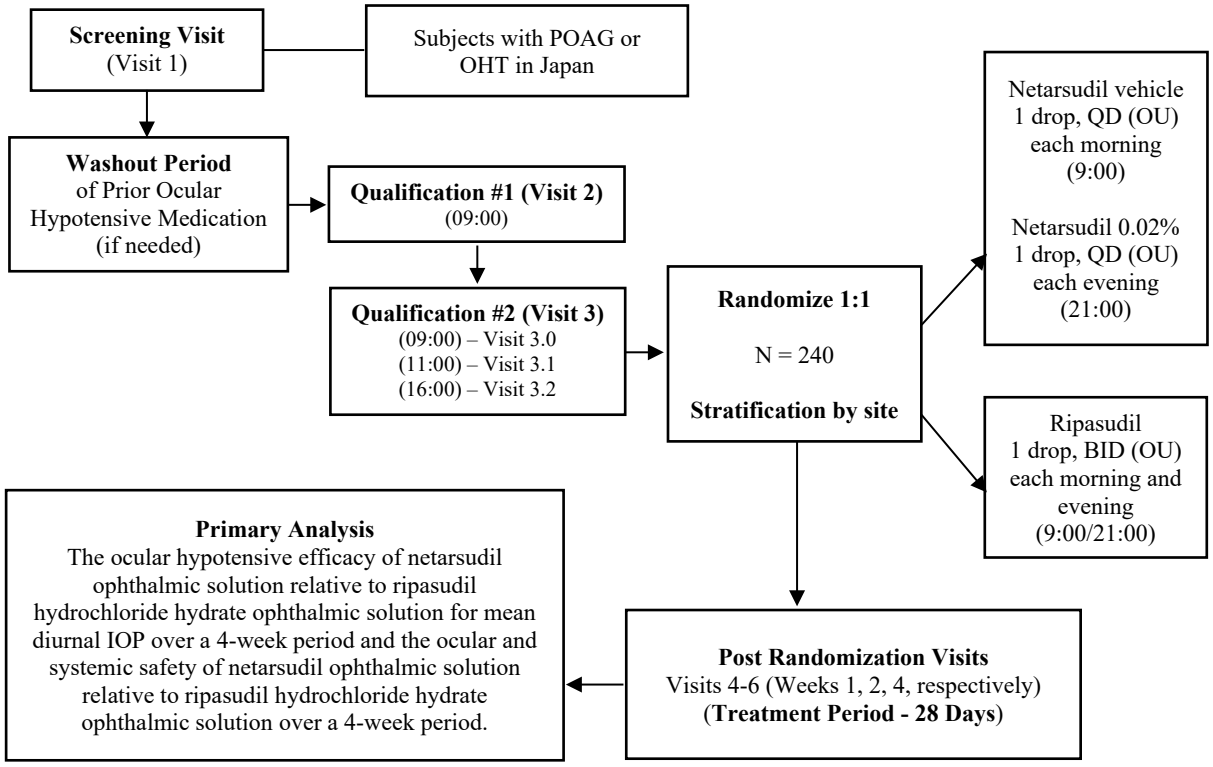
## 2.1 Primary Objective(s)

The objective of this study is:

- To evaluate the ocular hypotensive efficacy and safety of netarsudil ophthalmic solution 0.02% QD compared to the active comparator, ripasudil hydrochloride hydrate ophthalmic solution 0.4% BID, over a 4-week period (superiority study).

# 3. INVESTIGATIONAL PLAN

**Figure 1 Study Design**



## 3.1 Overall Study Design and Plan

This study will be a prospective, single-masked, randomized, multi-center, parallel-group, 4-week study evaluating the efficacy and safety of once daily (QD) netarsudil ophthalmic solution 0.02% compared to twice daily (BID) ripasudil hydrochloride hydrate ophthalmic solution 0.4% in Japanese subjects with POAG or OHT in Japan over a 4-week period.

Netarsudil ophthalmic solution 0.02% will be dosed QD (21:00) while ripasudil hydrochloride hydrate ophthalmic solution 0.4% will be dosed BID (9:00/21:00). In order to be adequately masked, subjects dosing with netarsudil ophthalmic solution 0.02% (21:00) also will dose with vehicle QD (9:00).

Subjects eligible to be enrolled in this study will be subjects with diagnosis of either POAG or OHT. Approximately 240 subjects will be enrolled in this study. Subjects who agree to participate in this study and are enrolled will attend a total of up to 6 study visits: 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 will be required to washout of their pre-study ocular hypotensive medication for a prescribed period (i.e., 5 days to 6 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 undergo additional testing at Qualification Visit #2. If deemed eligible, subjects will be enrolled at Qualification Visit #2 and assigned to either the netarsudil group or ripasudil group in a 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 study drug in both eyes BID in the morning (9:00 ± 1 hour) and in the evening (21:00 ± 1 hour) 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 pre-dose, 2 hours and 7 hours post-dose of the dose in the morning. 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

This is a randomized, single-masked, comparative study to confirm the superiority of netarsudil 0.02% QD to ripasudil hydrochloride hydrate ophthalmic solution 0.4% BID in patients with POAG or OHT. The primary efficacy endpoint of the study is mean diurnal IOP at Week 4.

The clinically optimal concentration of netarsudil was confirmed to be 0.02% in the Japanese Phase 2 study (AR-13324-CS208). Since QD dosing in the same study demonstrated a statistically significant difference from placebo, netarsudil will be administered once a day in the evening. The treatment period was set to be 4 weeks because both netarsudil and ripasudil exerted adequate reduction of IOP during 4 weeks of treatment (netarsudil Japanese Phase 2 study AR-13324-CS208 and non-Japanese Phase 3 studies AR-13324-CS301, AR-13324-CS302 and AR-13324-CS304, and ripasudil Japanese Phase 2 study K-115-03 and Japanese Phase 3 study K-115-05).

This study will use ripasudil hydrochloride hydrate ophthalmic solution 0.4% as a comparator. Ripasudil is positioned in the second-line treatment options after prostaglandin analogues (PGAs), a recommended first-line option in the treatment of glaucoma/OHT, according to the Japan Glaucoma Society Guidelines for Glaucoma (4th Edition). Also, ripasudil belongs to the same ROCK inhibitor class as netarsudil. Therefore, it was selected as a comparator in this study. A superiority study is planned as a confirmatory study, based on the results of study CS208 and Japanese Phase 2 dose-response study (K-115-03) and Japanese Phase 3 placebo-controlled study (K-115-05) of ripasudil for the patients with POAG or OHT.

While this study will be conducted under masked conditions to avoid biases in the efficacy and safety evaluations, a single-masked (evaluator-masked) design using different container closure systems between netarsudil and ripasudil was selected.

### 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 study drug for this study will start on the evening of Visit 3 (Qualification Visit #2; Day 1) and end on the morning of Visit 6 (Week 4/Day 29).

If a subject develops an AE during the 28-day treatment period, the duration of the study will continue until resolution or stabilization of the AE.

# 4. STUDY POPULATION SELECTION

## 4.1 Study Population

A total of approximately 240 Japanese subjects will be enrolled in this study at approximately 28 investigational sites in Japan comprising a total of 120 subjects per treatment arm for each of the 2 treatment arms. Subjects will be at least 20 years of age with diagnosed POAG or OHT, each of whom meets all inclusion criteria and none of the exclusion criteria.

Planned enrollment numbers are higher (240 total, 120 subjects per arm) than statistically required for demonstrating efficacy (approximately 93 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 240 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. 20 years of age or older

2. Diagnosis of POAG or OHT in both eyes (POAG in one eye and OHT in the fellow eye is acceptable)

3. Medicated intraocular pressure (IOP) ≥ 14 mmHg in at least one eye and < 30 mmHg in both eyes at screening visit (this also applies to treatment naive subjects)

4. For POAG eyes, unmedicated (post washout) IOP ≥ 15 mmHg and < 35 mmHg in the study eye at 2 qualification visits (09:00 hours), 2-7 days apart. At second qualification visit IOP ≥ 15 mmHg and < 35 mmHg at 11:00 and 16:00 hour (in the same eye).
   **Note: For purposes of determining eligibility of subjects to be enrolled, any non-integral mean IOP number should not be rounded**

5. For OHT eyes, unmedicated (post washout) IOP ≥ 22 mmHg and < 35 mmHg in the study eye at 2 qualification visits (09:00 hours), 2-7 days apart. At second qualification visit IOP ≥ 22 mmHg and < 35 mmHg at 11:00 and 16:00 hours (in the same eye)
   **Note: For purposes of determining eligibility of subjects to be enrolled, any non-integral mean IOP number should not be rounded**

6. BCVA +0.7 log MAR or better (20/100 Snellen or better or 0.20 or better in decimal unit) in each eye

7. Willingness and ability 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 a maximum of 8 weeks is not judged safe as it would put the subject at risk for further vision loss
2. Retinal diseases that may progress during the study period (e.g., Macular edema, retinal detachment, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, pathological myopia)
3. 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
4. Ocular hyperemia score of moderate (+ 2) or severe (+3) 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. Any corneal disease or condition in either eye that in the investigator's opinion, may confound assessment of the cornea
10. Current evidence of corneal deposits or cornea verticillata in either eye
11. Planned use of any prohibited concomitant medications in either eye during the study
12. Mean central corneal thickness greater than 620 μm in either eye at screening
13. Any abnormality preventing reliable Goldmann applanation tonometry of either eye (e.g., keratoconus)

14. Known hypersensitivity to any component of netarsudil ophthalmic solution 0.02%, ripasudil hydrochloride hydrate ophthalmic solution 0.4%, or to topical anesthetic

15. Cannot demonstrate proper delivery of the eye drop, or, in the principal investigator or co-investigator's opinion, unable to deliver the eye drop consistently

**Systemic:**

16. Clinically significant systemic disease which might interfere with the study or place the subject at risk

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

18. 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

19. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable birth control includes: condoms plus intrauterine devices or condoms plus oral hormonal contraceptives, double barrier methods (e.g., condoms with spermicidal gel plus diaphragms). Birth control must be continued for at least 30 days after the last dose of the study drug. 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 ophthalmic solution is a sterile, isotonic, buffered aqueous solution containing netarsudil (0.02%), boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.015%). The product formulations are adjusted to approximately pH 5.

### 5.1.2 Vehicle or Control Drug

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

As for control drug, ripasudil hydrochloride hydrate ophthalmic solution 0.4% is a commercially available product (GLANATEC® ophthalmic solution 0.4%) and contains benzalkonium chloride as preservative. The product formulations are adjusted from pH 5 to pH 7.

## 5.2 Treatments Administered

Subjects will be randomized to receive investigational product (IP) netarsudil ophthalmic solution (0.02%) or ripasudil hydrochloride hydrate ophthalmic solution 0.4% administered 1 drop into each eye. Netarsudil ophthalmic solution 0.02% will be dosed QD (21:00) while ripasudil hydrochloride hydrate ophthalmic solution 0.4% will be dosed BID (9:00/21:00). In order to be adequately masked, subjects dosing with netarsudil ophthalmic solution 0.02% (21:00) also will dose with vehicle QD (9:00).

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

Netarsudil ophthalmic solution 0.02% doses and treatment period selected for this study are based on two Phase 1 studies (AR-13324-CS103 and AR-13324-CS104) and the results of the completed Phase 2 study in Japan (AR-13324-CS208) and 4 Phase 3 studies (AR-13324-CS301, AR-13324-CS302, AR-13324-CS303 and AR-13324-CS304) completed outside Japan. Each dose is being administered QD OU in the evening (21:00 ± 1 hour) in this study, since this dosing regimen was found to provide good efficacy and tolerability in the previous clinical studies.

The control drug, ripasudil hydrochloride hydrate ophthalmic solution 0.4% will be dosed BID (9:00/21:00) according to the package insert (GLANATEC® PI).

## 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 ratio to receive netarsudil ophthalmic solution 0.02% or ripasudil hydrochloride hydrate ophthalmic solution 0.4% 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.

This study adopts a single-masked study design. Therefore, to ensure masked state to the investigators and the clinical study team, the study medication bottles are placed in a sealed kit so that the study medication cannot be identified from the outside of the kit. Study staff responsible for dispensing study medications must always prescribe a study medication to the subject in a sealed state and should instruct subjects that the study drug must be in the kit when it is returned. Unmasked staff responsible for collecting study medication ensures masked state to the investigators and the clinical study team by immediately sealing the collected study drug.

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 judges 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.

Prohibited medications include concurrent therapy of:

- Any form of ocular hypotensive medications (prescription or OTC)
- Miotics
- Epinephrine-related compounds
- Carbonic anhydrase inhibitors
- α-adrenoceptor agonists
- β-adrenoceptor antagonists
- Muscarinic agonists (e.g., pilocarpine)
- Ocular prostaglandin analogues
- Rho kinase inhibitors
- Any corticosteroid containing ocular or systemic drug 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 is allowed. 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. Subjects will be informed that benzalkonium chloride contained in this study drug as preservative agent has a risk to distain contact lenses.

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 |
|---|---|
| Rho kinase inhibitor | 6 weeks |
| 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. In addition, eye dilation may cause blurred vision and temporary sensitivity to light.

While pupils are dilated, subjects should protect eyes while in bright light by wearing sunglasses. Subjects should not drive or engage in any hazardous activity until vision returns to normal. 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 twice-daily dosing regimen. Dosing should occur in the morning (9:00 ± 1 hour) and in the evening (21:00 ± 1 hour). 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 morning and evening.

## 5.9 Packaging and Labeling

The container-closure systems for all products are multi-dose ophthalmic dropper dose bottles. The commercial label from ripasudil will be removed and replaced with an investigational label which will be similar in appearance for both treatment groups. The labeled bottles will be packaged in identical appearing subject kits to ensure adequate masking.

The container-closure system for the netarsudil ophthalmic solution 0.02% and vehicle in this clinical study is a clear, multi-dose low density polyethylene (LDPE) dropper dose ophthalmic bottle with a polypropylene white cap. The container for ripasudil hydrochloride hydrate ophthalmic solution 0.4% in this study is a clear multi-dose LDPE dropper dose ophthalmic bottle with deep green polypropylene cap. Each packaged unit will be labeled with an investigational label with the minimal information required per Japan regulatory requirements.

The products for each individual treatment assignment will be packaged into identical subject kits; each subject kit will contain 2 bottles of the assigned treatment: netarsudil ophthalmic solution 0.02% and vehicle, or ripasudil hydrochloride hydrate ophthalmic solution 0.4%. The two bottles contained in one kit will be identified as one for AM and one for PM.

## 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. Any study staff can dispense these medications. Only unmasked staff who is not involved in clinical evaluation of the subjects is allowed to collect the used/returned 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. Once the bottle is opened, the product must always be protected from light and is recommended to be stored in the carton provided. Subjects should be instructed not to freeze the product.

## 5.11 Study drug 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) or Independent Ethics Committee (IEC) 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 and staff are 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 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.

## 6.4 Ophthalmic Assessment

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 the Manual of Procedures (MOPs): visual acuity, visual field, IOP, biomicroscopy, central corneal thickness, gonioscopy, symptomatology, and dilated ophthalmoscopy.

The Investigator or designee will perform additional assessments for subjects with cornea verticillata as described in the MOPs: slit lamp examination and verticillata grading.

## 6.5 Vital Signs

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

## 6.6 Pregnancy testing (for women of childbearing potential)

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.

If the female partner of a subject become pregnant, the Investigator should collect information on the outcome of the pregnancy and the health of the baby (if applicable). The information will be reported to the sponsor to be used to understand the safety of the drug used during pregnancy.

## 6.7 Study Eye Selection Process

Subjects must qualify in the study eye based upon IOP, ocular history and exam. If the subject qualifies in only one eye, then this eye is designated the study eye. If the subject qualifies in both eyes, then the study eye will be the eye with the higher IOP at 09:00 hours on Visit 3. If both eyes have the same IOP at 09:00 hours on Visit 3, then the right eye will be the study eye. For each subject, BOTH eyes will be treated.

## 6.8 Dispensing Study Drug

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. Any study staff can dispense these medications. Only unmasked staff who is not involved in clinical evaluation of the subjects is allowed to collect the used/returned product by maintaining a study medication accountability log.

## 6.9 Efficacy Assessments

### 6.9.1 Specification of the Efficacy Parameters

The primary efficacy outcome will be the comparison of netarsudil ophthalmic solution 0.02% relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% 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 solution 0.02% relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% 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.

### 6.9.2 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.

### 6.9.3 Intraocular Pressure

Local anesthetic will 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. See MOPs for further information.

## 6.10 Safety Assessments

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

- Ocular symptoms/AEs
- BCVA
- 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/AEs
- Pregnancy testing (for women of childbearing potential)

### 6.10.1 Best-Corrected Visual Acuity (BCVA)

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 Landolt-C chart or its equivalents. See MOPs for details of the procedures to be followed when determining BCVA.

### 6.10.2 Biomicroscopy

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

#### 6.10.2.1 Corneal Deposit Grading under Biomicroscopy

Subjects who are diagnosed with cornea verticillata by slit lamp examination will undergo the evaluation for its location and grading using a published grading scale for amiodarone-induced cornea verticillata (Orlando 1984). See the MOPs for the details of this grading scale.

### 6.10.3 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 the MOPs.

### 6.10.4 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, Kowa etc.). SITA Standard is preferred, SITA fast or equivalent 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 blind spot should be turned on for all visual fields assessments in order to calculate the fixation losses. The gaze track should be turned on if gaze track is essential to assess fixation losses.** See MOPs for further information.

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

## 6.11 Adverse Events Assessments

### 6.11.1 Performing Adverse Event (AE) Assessments

Qualified study staff responsible for assessing 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 Week 4 [Day 29] or study discontinuation. 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.

If a subject has an ongoing AE at the time of study exit, the ongoing AE must be followed-up and provided appropriate medical care until the event has resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

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

### 6.11.2 Adverse Event Definition

The following definitions of terms apply to this section:

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

- *Suspected adverse reaction (SAR):* Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of clinical trial notification (CTN) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

- *Life-threatening AE or life-threatening 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 suspected serious 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.

- *Unexpected AE or unexpected SAR*. An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or the package insert of GLANATEC® ophthalmic solution 0.4% 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: 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.

### 6.11.3 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 Week 4 [Day 29] or study discontinuation. If a subject has 1 or more ongoing AEs at the time of study exit, the subject must be followed and provided appropriate medical care until the event is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event. These follow-up visits will be documented.

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

**1. Action Taken with Study Drug:**

- None
- Study Drug Discontinued
- Study Drug 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

### 6.11.4 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.

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 6.11.7 for further information on serious events).

### 6.11.5 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.

### 6.11.6 Expectedness

The most frequently reported AE for netarsudil ophthalmic solution in two Phase 2 and four Phase 3 studies (Clinical Study Reports AR-13324-CS205, AR-13324-CS208, AR-13324-CS301, AR-13324-CS302, AR-13324-CS303 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 conjunctival hemorrhage, and cornea verticillata (corneal deposits) which did not affect visual function.

An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or the package insert of GLANATEC® ophthalmic solution 0.4% 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 and adverse reactions that are both unexpected and serious should be reported in an expedited fashion to the Sponsor (see Section 6.11.7.2 for further details).

### 6.11.7 Serious Adverse Events (SAEs), Suspected Serious Adverse Reactions (SSARs), Suspected Unexpected Serious Adverse Reactions (SUSARs)

#### 6.11.7.1 Reporting SAEs or SSARs

An Investigator must immediately (i.e., within 24 hours) report any SAE or SSAR (see Section 6.11.2 for definitions) to the representative of contract research organization (CRO) of the Sponsor (see Section 6.11.7.3 for contact information), whether or not the SAE or SSAR is considered drug-related, including those listed in the Investigator's Brochure or the package insert of GLANATEC® ophthalmic solution 0.4%. 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 or is observed during the study or at a subject's last study visit.

SAEs and SSARs must be reported to the IRB according to the IRB requirements.

#### 6.11.7.2 Reporting SUSARs

The Investigator must immediately (i.e., within 24 hours) report SUSARs that occur or are observed during the course of the study or at the subject's last study visit. In the event of a SUSAR, the site must notify the representative of CRO of the Sponsor by telephone within 24 hours of knowledge of the event, whether or not complete information is available. In the case of incomplete information, the Investigator must provide follow-up information as soon as possible using the SAE report form.

#### 6.11.7.3 Safety Reporting Contact Information

The Investigator must report an SAE, SSAR, or SUSAR occurring at his/her site to the representative of CRO of the Sponsor regardless of causality.

[redacted]

[redacted]

## 6.12 Pregnancy Reporting

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 representative of CRO of the Sponsor. 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 (see Section 6.11.7.3 for contact information). Following delivery or termination of pregnancy, the pregnancy report form is to be completed and submitted by fax or email to the representative of CRO of the Sponsor.

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

## 6.13 Removal of Subjects from the Study or Study Treatment

### 6.13.1 Completed Subject

A completed subject is defined as one who completes all planned study treatments and visits and completion of the post-treatment follow-up visit procedures.

### 6.13.2 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. During the treatment period, 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**

### 6.13.3 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.

For subjects who choose to withdraw consent or who are discontinued for non-compliance prior to completing the treatment period, 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.

### 6.13.4 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.

### 6.13.5 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.

## 6.14 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:

- Heart rate and blood pressure
- Pregnancy test: All females of childbearing potential must have a negative urine pregnancy test result
- BCVA
- Central corneal thickness will be measured by pachymetry (taken at screening or within 1 week prior to the Screening Visit)
- IOP (before pupil dilation): Medicated IOP must be ≥ 14 mmHg in at least one eye 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?"

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 IOP and safety measurements at 09:00 hours)

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.

The following procedures will be performed:

- Heart rate and blood pressure
- Symptomatology: Individuals will be asked "How are you feeling?"
- BCVA
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured between 09:00 and 09:30 hours.

For further evaluation of POAG eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 15 mmHg and < 35 mmHg in the study 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 study eye. **This is the first of the four qualifying IOPs for randomization.**

Individuals who do NOT meet the IOP requirements above due to a low IOP 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 09:00 hours)

Within 2 to 7 days after Visit 2, individuals will return to the Investigator's office for the next 09:00 hour IOP measurement.

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?"
- BCVA
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured between 09:00 and 09:30 hours.

For further evaluation of POAG eyes in the study, at this time, unmedicated (post washout) IOP must be ≥ 15 mmHg and < 35 mmHg in the study 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 study eye. **This is the second of the four qualifying IOPs for randomization.**

Qualified individuals will continue with the measurements of IOP at 11:00 hours and 16:00 hours.

Individuals who do NOT meet the IOP requirements above due to a low IOP 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 09:00, 11:00, 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 11:00 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 between 11:00 to 11:30 hours.

For further evaluation of POAG 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. **This is the third of the four qualifying IOPs for randomization.**

Qualified individuals will continue with the qualification visit. Individuals who do NOT meet this requirement due to low IOP 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 09:00, 11:00 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 between 15:30 and 16:30 hours.

For further evaluation of POAG 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. **This is the fourth of the four qualifying IOPs for randomization.**

Individuals who do NOT meet this requirement due to low IOP 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 09:00, 11:00 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 at least one eye based upon IOP and ocular history and exam; for a subject who qualifies in only one eye, this eye is designated the study eye. If the subject qualifies in both eyes, then the study eye will be the eye with the higher IOP at 09:00 hours on Visit 3. If both eyes have the same IOP at 09:00 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 in the morning (9:00 ± 1 hour) and in the evening (21:00 ± 1 hour)

- Instructed to return to the office with their study medication in the kit on Visit 4 (Week 1 [Day 8])

- **Instructed not to administer their masked medication OU at home on the morning of the next visit (Visit 4)**

A window of ± 2 days for Visit 4 is permitted.

### 7.3.4 Visit 4.0 (Week 1 [Day 8], for IOP and safety measurements at 09:00 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
- BCVA
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured between 09:00 and 09:30 hours.

**Subjects are allowed to administer their masked medication after IOP measurements.**

Any new or worsening of symptoms from the time the subject receives the first dose of study medication 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 11:00 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 2 hours (± 30 mins) post-dose of the dose in the morning (Visit 4.0)**.

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 7 hours (± 30 mins) post-dose of the dose in the morning (Visit 4.0)**.

Subjects will be:

- Instructed to continue to administer their study medication at home in the morning (9:00 ± 1 hour) and in the evening (21:00 ± 1 hour)
- Instructed to return to the office with their used study medication in the kit on Visit 5 (Week 2 [Day 15])
- **Instructed not to administer their masked medication OU at home on the morning of the next visit (Visit 5)**

A window of ± 3 days for Visit 5 is permitted.

### 7.3.7 Visit 5.0 (Week 2 [Day 15], for IOP and safety measurements at 09:00 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
- BCVA
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy. IOP must be measured between 09:00 and 09:30 hours.

**Subjects are allowed to administer their masked medication after IOP measurements.**

Any new or worsening of symptoms from the time the subject receives the first dose of study medication 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 11:00 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 2 hours (± 30 mins) post-dose of the dose in the morning (Visit 5.0)**.

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 7 hours (± 30 mins) post-dose of the dose in the morning (Visit 5.0)**.

Subjects will be:

- Instructed to continue to administer their masked medication at home in the morning (9:00 ± 1 hour) and in the evening (21:00 ± 1 hour)
- Instructed to return to the office with their study medication in the kit on Visit 6.0 (Week 4 [Day 29])
- **Instructed not to administer their masked medication OU at home on the morning of the next visit (Visit 6)**

A window of ± 3 days for Visit 6 is permitted.

### 7.3.10 Visit 6.0 (Week 4 [Day 29], for IOP and safety measurements at 09:00 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 childbearing potential may be performed at any time point throughout Visit 6)
- BCVA
- A non-dilated eye examination will be performed, including IOP and biomicroscopy. IOP must be measured 9:00 and 9:30 hours.

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

Any new or worsening of symptoms from the time the subject receives the first dose of study medication 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 11:00 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 2 hours (± 30 mins) post-dose of the dose in the morning (Visit 6.0)**.

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 7 hours (± 30 mins) post-dose of the dose in the morning (Visit 6.0)**.

- 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 AEs in the CRF.

## 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

Summaries will be presented by treatment, visit, and time point (as applicable). Continuous and ordinal study assessments will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Discrete study assessments will be summarized 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% QD and ripasudil 0.4% BID will be calculated as netarsudil – ripasudil.

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

For diurnally-adjusted IOP, baseline will refer to the time-relevant measure at Visit 3.0 and 3.1 (e.g., IOP at 09:00 hours at Visit 3.0 will be the baseline for 09:00 hours at Visit 4.0, Visit 5.0, and Visit 6.0; IOP at 11:00 hours at Visit 3.1 will be the baseline for 11:00 hours at Visit 4.1, Visit 5.1, and Visit 6.1; etc.). For all other variables, baseline is defined as the last non-missing 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.

Change from baseline will be calculated as: follow-up minus baseline.

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 diurnal baseline 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.

The unit of analysis for efficacy will be the study eye. If the subject qualifies in only one eye, then this eye is designated the study eye. If the subject qualifies in both eyes, then the study eye will be the eye with the higher IOP at 09:00 hours on Visit 3. If both eyes have the same IOP at 09:00 hours on Visit 3.0, then the right eye will be the study eye. For each subject, BOTH eyes will be treated. Safety will be summarized at the eye level (study eyes and fellow eyes separately) for measures captured at the eye level and at the subject level for measures not captured at the eye level. Adverse events (AEs) will be summarized at the subject level, counting a subject as having had an ocular AE if the subject has the ocular AE in either eye.

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

## 9.2 Hypotheses

$H_0$: The difference in mean diurnal IOP in study eyes treated with netarsudil QD versus study eyes treated with ripasudil BID (netarsudil QD – ripasudil BID) at Week 4 = 0.

$H_1$: The difference in mean diurnal IOP in study eyes treated with netarsudil QD versus study eyes treated with ripasudil BID (netarsudil QD – ripasudil BID) at Week 4 ≠ 0.

## 9.3 Adjustments for Multiplicity

No adjustment for multiplicity is required for this study with a single primary endpoint and no secondary endpoints identified for labeling claims.

## 9.4 Determination of Sample Size

Ninety three (93) subjects (study eyes) per treatment group are required to have 90% power (1-β) to reject H0 in favor of H1 at a two-sided significance level of 5%, assuming that a

difference of the change from baseline in mean diurnal IOP (netarsudil QD – ripasudil BID) in the proposed study is -1.1 mmHg with a common standard deviation of 2.3. The target sample size is set to 120 per treatment group to allow for withdrawals and dropouts.
Note that change from baseline values from historic studies are being used as estimates from which to calculate sample size for a non-change from baseline primary endpoint due to the change from baseline estimates for standard deviation better reflecting the standard deviation obtained from the primary analysis strategy within this study.

## 9.5 Analysis Populations

### 9.5.1 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.

### 9.5.2 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.

### 9.5.3 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.

## 9.6 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.

## 9.7 Primary Efficacy

### 9.7.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint will be the comparison of netarsudil ophthalmic solution 0.02% relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% for mean diurnal IOP within a treatment group at Week 4 (Day 29) by Goldmann Applanation Tonometry.

### 9.7.2 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 and regression based multiple imputation techniques used to impute missing data. The least squares mean difference (netarsudil QD – ripasudil BID) will be presented as well as the 2-sided p-value and 95% confidence interval (CI). Inference will be made on the 2-sided p value. Superiority of netarsudil QD over ripasudil BID will be concluded if the 2-sided p-value, for testing the difference (netarsudil QD – ripasudil BID) to 0, $\leq 0.05$ and the point estimate of the difference $< 0$.

Analyses will be performed primarily on the ITT population using the following strategy to handle intercurrent events:

Intercurrent event strategy:

- Discontinuation of study drug and non-optimal compliance will be ignored; IOP will continue to be measured and used [treatment policy strategy].

- Withdrawal due to lack of efficacy or adverse event: missing data will be imputed employing Multiple Imputation (MI) assuming missing not at random using: Control-based regression methodology [hypothetical strategy].

- Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse event: missing data will be imputed employing Multiple Imputation (MI) assuming missing at random using randomized treatment-based regression methodology [hypothetical strategy].

Sensitivity analyses will be performed on observed data only and where worst on treatment time-relevant observation within a subject is carried forward for withdrawal due to lack of efficacy or adverse event and last time consistent observation within a subject is carried forward for other missing data.

## 9.8 Secondary Efficacy

### 9.8.1 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. Qualifying fellow eyes will be evaluated separately for the primary analysis of the primary efficacy measure.

### 9.8.2 Secondary Efficacy Analyses

Secondary analyses of the primary efficacy endpoint include repeating the primary analysis strategy using: observed data only, last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures, and using worst on treatment time-relevant observation within a subject carried forward for withdrawal due to lack of efficacy or adverse event and last time-relevant observation within a subject carried forward for other missing data. 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% QD versus ripasudil 0.4% BID 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 (09:00, 11:00, 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 a 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% QD and ripasudil 0.4% BID at each time point and visit, including two-sample t-tests and 95% t-distribution confidence intervals on the difference (netarsudil - ripasudil).

Sub-group analyses based upon pre-study characteristics such as site, demographics, baseline IOP categories, 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 ≥ 0 to ≥ 10 mmHg in 2 mmHg increments and percent reduction from baseline of ≥ 5% to ≥ 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 ≤ 24 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% QD versus ripasudil 0.4% BID for each category at each visit. These analyses will be presented for both the ITT and PP populations with observed data only.

## 9.9 Safety

### 9.9.1 Safety Endpoints

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

- Ocular symptoms/AEs
- BCVA
- 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/AEs
- Pregnancy testing (for women of childbearing potential)

### 9.9.2 Safety Analyses

Verbatim descriptions of AEs will be mapped to MedDRA/J thesaurus terms and be presented in a data listing. Treatment emergent AEs (TEAEs), those that occur or worsen 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 TEAEs. These summaries will also be presented for TEAEs related 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% vs ripasudil hydrochloride hydrate ophthalmic solution 0.4%.

Best-corrected visual acuity data for both the study eye and the fellow eye will be summarized for each visit and for change from baseline to each post-treatment visit using the continuous summary statistics.

Slit lamp biomicroscopy and dilated ophthalmoscopy measures will be summarized at each measured visit and 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). Additionally for slit lamp biomicroscopy, discrete summaries will be provided by region, finding, visit, time point, and eye (study eye and fellow eye) for the number of subjects with at least one severity grade increase from baseline and for the number of subjects judged to be clinically significant by the Investigator. Fisher's exact tests will be used to compare incidence between treatment groups in both tables.

Cup-to-disc ratio will be summarized at each measured visit and for change from baseline to each measured visit using continuous summary statistics by treatment group and visit.

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

## 9.10 Other Assessments or Analyses

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

## 9.11 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 or Independent Ethics Committee Approval

This study is to be conducted in accordance with IRB or IEC regulations and ICH-GCP and J-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) or IEC(s) for review and approval. This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB or IEC prior to initiation of the study. Original letter from the IRB or IEC 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 or IEC 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.

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

## 10.3 Ethical Conduct of the Study

The study will be conducted according to ethical principles based on the Declaration of Helsinki and the guidance stipulated in Article 14, Paragraph 3, and Article 80 2 of the Pharmaceuticals, Medical devices and Other Therapeutic Products Act of Japan, Ministry of Health, Labor and Welfare (MHLW) Ordinance on Good Clinical Practice (MHLW Ordinance No 28 (27 March 1997).

## 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 legal guardian prior to enrollment into the study in accordance with local regulatory requirements.

All ICFs must be approved for use by the Sponsor or Sponsor representative and receive approval/favorable opinion from an IRB or IEC prior to their use. If the consent form

requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the Sponsor or Sponsor representative prior to submission to the governing IRB or IEC 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 or IEC.

## 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 regulations.

Monitors, auditors and other authorized representatives of Aerie, the IRB(s) or IEC(s) approving this study, and government regulatory authorities (e.g., PMDA 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 including but not limited to 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 should be stored in a secure environment. 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), and local 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 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 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

All study related correspondence, patient records, consent forms, patient privacy documentation, records of distribution and use of all study drugs, and copies of eCRFs should be maintained on file.

In Japan, the records should be retained until the day on which marketing approval of the test drug is obtained or 3 years after the date of premature termination or completion of the clinical trial, whichever comes later.

For countries falling within the scope of the ICH guidelines, study related documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH region

or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, if required by the applicable regulatory requirements or if needed by Aerie Pharmaceuticals.

For countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

### 10.12 Financial Disclosure

The Principal Investigator and sub-Investigators 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.

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### 11.2 Internal References

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2. [redacted]
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4. [redacted]
5. [redacted]
6. [redacted]

7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]

## Appendix 1 Schedule of Visits and Procedures

| | | | | | | **Post Day 1 Treatment[1]** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day (D)/Week (W) | Screening | Qual. #1 | Qual. #2 (Day 1) | | | W1 (Day 8±2) | | | W2 (Day 15±3) | | | W4[2] (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) | -- | 09 | 09 | 11 | 16 | 09 | 11 | 16 | 09 | 11 | 16 | 09 | 11 | 16 |
| Informed Consent | X | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | X | X | X | X | | | | | | | | | |
| Washout[3] | X | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | |
| Medical/Ophthalmic History | X | X | X | | | | | | | | | | | |
| Concomitant Medications | X | X | X | | | X | | | X | | | X | | |
| Vital Signs (heart rate, blood pressure) | X | X | X | | | X | | | X | | | X | | |
| Urine Pregnancy Test[4] | X | | | | | | | | | | | X | | |
| Symptoms/AEs[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| BCVA[6] | X | X | X | | | X | | | X | | | X | | |
| IOP | X | X[7] | X[7] | X[7] | X[7] | 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[8] / Pachymetry[9] | G/P | | | | | | | | | | | | | |
| Visual Field[10] | X | | | | | | | | | | | | | |
| Ophthalmoscopy (dilated) | X | | | | | | | | | | | | | X |
| Eye-Drop Instillation Evaluation | X | | | | | | | | | | | | | |
| Study Medications Dispensed | | | | | X | | | | | | | | | |
| Study Medications Collected | | | | | | | | | | | | X[11] | | |
| Study Completed | | | | | | | | | | | | | | X |

## Appendix 1 Schedule of Visits and Procedures (cont'd)

Abbreviations: AE = adverse event; BCVA = best corrected visual acuity; IOP = Intraocular pressure.
Early Discontinuation: Visit 6.0 procedures are to be completed plus a dilated ophthalmoscopy examination.
Visit Requirements: There is no visit time requirement for Visit 1 (Screening). For Visit 2, IOP measurements will be 09:00 (+30 mins). For Visit 3, IOP will be measured at 09:00 (+30 mins), 11:00 (+30 mins) and 16:00 (±30 mins) hours. During Post Day 1 (Visit 4, 5, and 6) Treatment visits, study medication at 9:00 on the day of the visit will be administered after IOP measurements at 9:00 (+30 mins).
Two subsequent IOP measurements will be taken 2 hours (±30 mins) and 7 hours (±30mins) after the study medication in the morning, respectively.

1. If subjects develop cornea verticillata at Post Day 1 Treatment (visit 4 to visit 6), additional evaluation of grading and location (e.g. epithelium, stroma, or endothelium) of Cornea verticillata will be conducted in parallel.
2. 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.
3. Subjects currently using ocular hypotensive medications must undergo a minimum washout period.

| Medication Class | Minimum Washout Period |
|---|---|
| Rho kinase inhibitor | 6 weeks |
| 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 |

4. Urine pregnancy test for women of childbearing potential is required.
5. 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 09:00, 11:00, and 16:00 hours) as needed.
6. BCVA testing should precede IOP measurement, the administration of topical anesthetic agents, or any examination requiring contact with the anterior segment.
7. Individuals returning at an Unscheduled Visit within 1 week to re-attempt IOP qualification are required to only re-measure IOP in both eyes.
8. Gonioscopy evaluation up to 3 months prior to randomization is acceptable.
9. Pachymetry within 1 week prior to screening is acceptable.
10. 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.
11. Collect kit(s) dispensed during the Day 1 visit, after dosing their masked medication in the morning.

## Appendix 2 Sponsor's Obligations

Aerie Pharmaceuticals 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 study drug 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 6.11, 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 documents that state the financial interests and arrangements of clinical investigators

## Appendix 3 Investigator's Obligations

The Investigator is obligated to:

1. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Investigator is responsible for notifying the Sponsor Safety Officer immediately (see Section 6.11, Adverse Events Assessments). The Investigator must also notify the Sponsor Representative and the IRB to which he/she is responsible.
2. Prior to initiating the study, sign and return to the Sponsor Representative all the relevant forms required by local regulatory agency (e.g. 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 should be included upon local regulation requirements
3. Cooperate with the Sponsor on the preparation of documents in which financial interests and arrangements of clinical investigators are disclosed
4. Obtain and submit to the Sponsor a copy of his/her IRB approval of the protocol prior to initiating the study.
5. Obtain signed informed consent from each subject or his/her legal guardian prior to acceptance of the subject into the study.
6. Read and agree to adhere to the study protocol prior to the initiation of the study. Deviations from the study protocol are not to be implemented without the prior written approval of the Sponsor and IRB, unless protection of the safety and welfare of study subjects requires prompt action. During the study, if the Investigator feels that in his/her clinical judgment, it is necessary to promptly terminate 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.
7. Accurately record, at the Investigator's site, all required data on each subject's CRF.
8. Keep accurate records of the number of study medication or device units received from the Sponsor and dispensed or administered to each subject during the study, and return any unused study medication or devices to the Sponsor at the completion of the study. Before returning the study medications or devices to the Sponsor, a detailed inventory should be recorded and placed in the Investigator's file.
9. Assure that 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.

10. 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.
11. Provide the governing IRB with a brief (i.e., 1 to 3 pages) Investigator's summary within 90 working days of the study completion.
12. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study.
13. Maintenance of records:
    a) Disposition of drug. An Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the Investigator shall return the unused supplies of the drug to the Sponsor, or otherwise provide for disposition of the unused supplies of the drug.
    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. In Japan, the records should be retained until the day on which marketing approval of the test drug is obtained or 3 years after the date of premature termination or completion of the clinical trial, whichever comes later.

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 4 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 5 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 Protocol Amendment

### AMENDMENT 1: 11 January 2021

- Modified or added text:
  - Cover page:
    - ADDED: ClinicalTrials.gov Identifier: NCT04620135
  - Synopsis Study Design and Section 3.1 Overall Study Design and Plan:
    - WAS: Approximately 208 subjects will be enrolled in this study.
    - IS: Approximately **240** subjects will be enrolled in this study.
  - Synopsis Study Population:
    - WAS: A total of approximately 208 subjects will be enrolled in this study at approximately 25 clinical sites, comprising a total of 104 subjects per treatment arm for each of two treatment arms.
    - IS: A total of approximately **240** subjects will be enrolled in this study at approximately **28** clinical sites, comprising a total of **120** subjects per treatment arm for each of two treatment arms.
  - Synopsis Exclusion Criteria and Section 4.3 Exclusion Criteria:
    - ADDED: 2. Retinal diseases that may progress during the study period (e.g., Macular edema, retinal detachment, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, pathological myopia)
  - Synopsis Statistical Methods and Section 9.4 Determination of Sample Size:
    - WAS: The target sample size is set to 104 per treatment group to allow for withdrawals and dropouts.
    - IS: The target sample size is set to **120** per treatment group to allow for withdrawals and dropouts.
  - Section 3. INVESTIGATIONAL PLAN Figure 1:
    - WAS: N = 208
    - IS: N = **240**
  - Section 4.1. Study Population:

- WAS: A total of approximately 208 Japanese subjects will be enrolled in this study at approximately 25 investigational sites in Japan comprising a total of 104 subjects per treatment arm for each of the 2 treatment arms.

  Planned enrollment numbers are higher (208 total, 104 subjects per arm) than statistically required for demonstrating efficacy (approximately 93 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 208 subjects) is to be undertaken only after communication between the investigational site and the Sponsor representative.

- IS: A total of approximately **240** Japanese subjects will be enrolled in this study at approximately **28** investigational sites in Japan comprising a total of **120** subjects per treatment arm for each of the 2 treatment arms.

  Planned enrollment numbers are higher (**240** total, **120** subjects per arm) than statistically required for demonstrating efficacy (approximately 93 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 **240** subjects) is to be undertaken only after communication between the investigational site and the Sponsor representative.

- Section 6.10. Safety Assessments and Section 9.9.1 Safety Endpoints:
  - WAS: Systemic safety assessments as measured by heart rate, blood pressure
  - IS: Systemic safety assessments as measured by heart rate, blood pressure/**AEs**
- Section 6.11.7.3 Safety Reporting Contact Information:
  - [redacted]
  - [redacted]
- Section 7.3.3 Visit 3.2:
  - BOLD FORMATTING APPLIED: **Instructed not to administer their masked medication OU at home on the morning of the next visit (Visit 4)**
- Section 7.3.4 Visit 4.0 and Section 7.3.7 Visit 5.0:
  - BOLD FORMATTING APPLIED: **Subjects are allowed to administer their masked medication after IOP measurements.**

- Section 7.3.6 Visit 4.2:
  - BOLD FORMATTING APPLIED: **Instructed not to administer their masked medication OU at home on the morning of the next visit (Visit 5)**
- Section 7.3.9 Visit 5.2:
  - BOLD FORMATTING APPLIED: **Instructed not to administer their masked medication OU at home on the morning of the next visit (Visit 6)**
- Appendix 2 Sponsor's Obligations C and Appendix 3 Investigator's Obligations 1:
  - WAS: (see Section 6.10.1, Adverse Events Assessments).
  - IS: (see Section 6.11, Adverse Events Assessments).