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

Version 1 dated 26 August 2021

STATISTICAL ANALYSIS PLAN

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)

Sponsor: Aerie Pharmaceuticals Ireland Limited

Protocol Number: AR-13324-CS305

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Date: 26AUG2021

Version: 1.0

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SAP Date: **26AUG2021**

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Signing Reason: I am the author of this document
Signing Time: 30-Aug-2021 | 09:44 MST
6ADE4C31A60F4E3C8B0DF41A2BC71B6C

30-Aug-2021 | 09:44 MST

[redacted]

Date

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Signing Time: 30-Aug-2021 | 11:13 MST
2A777B73090F4723971C0CEA248F8C1D

30-Aug-2021 | 11:13 MST

[redacted]

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Signing Reason: I approve this document
Signing Time: 30-Aug-2021 | 23:20 EDT
5434888FA63D46E5B41CAB2FF0FF2638

30-Aug-2021 | 23:20 EDT

[redacted]

Date

Approved by: DocuSigned by: [redacted]
Signing Reason: I approve this document
Signing Time: 01-Sep-2021 | 21:27 EDT
AD671DEB78B641B480105F88CC4EEC58

01-Sep-2021 | 21:27 EDT
Date

[redacted]

Approved by: DocuSigned by: [redacted]
Signing Reason: I approve this document
Signing Time: 31-Aug-2021 | 07:54 EDT
D31A663F730F4A808E6630BC6595E314

31-Aug-2021 | 07:54 EDT
Date

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Table of Contents

List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BID	*Bis in die* (Twice Daily)
CI	Confidence Interval
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LS	Least Squares
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing Not at Random
NCS	Not Clinically Significant
ODO	Observed Data Only
OHT	Ocular Hypertension
PDF	Portable Document Format
POAG	Primary Open Angle Glaucoma
PP	Per Protocol
PT	Preferred Term
QD	*Quaque die* (Once Daily)
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol AR-13324-CS305, version Rev 1 dated 11JAN2021.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

2.1 Primary Objective

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

3. Efficacy Assessments

3.1 Primary Endpoint

- Comparison of netarsudil ophthalmic solution 0.02% relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% for mean of mean diurnal intraocular pressure (IOP) within a treatment at Week 4 (Day 29) by Goldmann Applanation Tonometry.

3.2 Secondary Endpoints

Secondary efficacy outcomes will be comparison of netarsudil ophthalmic solution 0.02% relative to ripasudil hydrochloride hydrate ophthalmic solution 0.4% for:

- Mean of 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 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

3.3 Safety Assessments

The safety of netarsudil ophthalmic solution 0.02% and ripasudil hydrochloride hydrate ophthalmic solution 0.04% will be evaluated in both eyes and will include the following:

- Ophthalmic and systemic adverse events (AEs)
- Best corrected visual acuity (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
- Systemic safety assessments as measured by heart rate and blood pressure
- Pregnancy testing (for women of childbearing potential)

3.4 Statistical Hypotheses

The null and alternative hypotheses, based on the primary variables, are as follows:

H_0: The difference in mean of 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 of 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.

3.5 Estimands

3.5.1 Primary Estimand

The primary comparison in this trial will be between netarsudil ophthalmic solution 0.02% and ripasudil hydrochloride hydrate ophthalmic solution 0.04% at Week 4 in the intent-to-treat (ITT) population with intercurrent events handled as described in the following estimand:

- Population: subjects with primary open angle glaucoma (POAG) or ocular hypertension (OHT) as defined through enrollment criteria
- Endpoint:
  - Mean of mean diurnal IOP (average over 09:00, 11:00, and 16:00 hour time points) (mmHg) at Week 4 Visit in the study eye
- Intercurrent event:
  - 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 AE: missing data will be imputed employing Multiple Imputation (MI) assuming missing not at random (MNAR) using control-based regression methodology [hypothetical strategy].
  - Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or AE: missing data will be imputed employing MI assuming missing at random (MAR) using randomized treatment-based regression methodology [hypothetical strategy].
- Population-level summary:

- The difference (netarsudil QD – ripasudil BID) in mean of mean diurnal IOP at Week 4 between study eyes treated with netarsudil QD and ripasudil BID.

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

4. Study Design and Procedures

4.1 General 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 QD netarsudil ophthalmic solution 0.02% compared to 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 a 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 #1, Qualification #2 (Day 1), 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 Week 4 (Day 29) visit. Procedures conducted at each of study Visits 4-6 will include safety measures and efficacy measurements, including IOP assessments. At Week 1 (Day 8), Week 2 (Day 15), and Week 4 (Day 29) visit, IOP will be assessed at pre-dose, and 2 hours and 7 hours post-dose of the dose in the morning. Following completion of the Week 4 (Day 29) 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 Week 4 (Day 29) visit and dilated ophthalmoscopy.

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule.

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is shown below.

						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

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 Day1 visit, after dosing their masked medication in the morning.

5. Study Treatments

Subjects meeting all eligibility criteria will be randomized 1:1 to one of the following two treatment groups:

Netarsudil ophthalmic solution 0.02%

- Vehicle dose in each eye QD (9:00) and netarsudil ophthalmia solution 0.02% dose in each eye QD (21:00) for approximately 28 days.

Ripasudil hydrochloride hydrate ophthalmic solution 0.4%

- Dosed BID (9:00/21:00) for approximately 28 days.

5.1 Method of Assigning Subjects to Treatment Groups

Approximately 240 subjects will be randomized in this study using IWRS methodology and will stratify subjects by site using a dynamic blocking design to maintain balance across treatment groups. Study medications will be allocated via the IWRS.

5.2 Masking and Unmasking

This study will be conducted in a single-masked where 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.

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 locked.

If the Investigator judges that 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 maintaining 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. 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.

6. Sample Size and Power Considerations

Ninety three (93) subjects (study eyes) per treatment group are required to have 90% power (1-β) to reject H_0 in favor of H_1 at a 2-sided significance level of 5%, assuming that a difference of the mean change from baseline in mean diurnal IOP (netarsudil QD – ripasudil BID) in the proposed study is -1.1 mmHg with a common standard deviation (SD) of 2.3. The target sample size is set to 120 subjects 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 SD better reflecting the SD obtained from the primary analysis strategy within this study.

7. Data Preparation

7.1 Input Data

Study data will be recorded on the electronic case report forms (eCRF) supplied by Statistics & Data Corporation (SDC) using Rave 2020.3.1. The treatment assignment data is not captured directly within the Rave system but is obtained from Suvoda, an external vendor; no other data will be obtained from external vendors.

When all prerequisites for database lock have been met, including availability of all masked data, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred, including receipt of written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7.2 Output Data

Data from the Rave system and external treatment assignment data will be transferred to Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

Output data will use the latest applicable SDTM and ADaM models and guidelines and will be validated with the latest Pinnacle 21 version. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

8. Analysis Populations

8.1 Intent-to-Treat

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.

8.2 Per Protocol

The per protocol (PP) population is a subset of the ITT population and 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.

8.3 Safety

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. General Statistical Considerations

9.1 Unit of Analysis

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 will be summarized at the subject level, counting a subject as having an ocular AE if the subject has the ocular AE in either eye.

9.2 Missing or Inconclusive Data Handling

Analyses of all efficacy endpoints will be performed primarily using the ITT population with MI techniques to impute missing data (where missing data for withdrawal due to lack of efficacy or AE will be imputed using control-based monotone regression, and missing data for all other reasons will be imputed using randomized treatment-based monotone regression). Sensitivity analysis of the primary endpoint will also be completed using ODO and where the worst on treatment time-consistent observation within a subject is

carried forward for withdrawal due to lack of efficacy or AE and the last time-consistent observation within a subject is carried forward for other missing data. Imputation will only be performed on missing data for the study eye at post-baseline scheduled visits; no imputation will be performed for fellow eye data or unscheduled post-baseline visits.

Analyses of safety endpoints will be performed using the Safety population, and there will be no imputation of missing data other than for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc).

Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

9.3 Definition of Baseline

For diurnally adjusted IOP and biomicroscopy, baseline will refer to the time-consistent measure at Visit 3 (e.g., IOP at 09:00 at Qualification Visit #2 will be the baseline for 09:00 at Week 2 and Week 4 visits; IOP at 11:00 at Qualification Visit #2 will be the baseline for 11:00 at Week 2 and Week 4 visits). For all other variables, baseline is defined as the last measurement prior to the first dose of study medication. An additional definition of baseline for conjunctival hyperemia will also be used: baseline (pre-washout) will be defined as the conjunctival hyperemia measure at Visit 1. Change from baseline will be calculated as follow-up visit – baseline visit.

9.4 Data Analysis Conventions

All final data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. Unless otherwise specified, all study data for treated subjects will be listed by treatment group, subject number, visit, and parameter as applicable.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, SD, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

All statistical tests will be 2-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Where applicable, 2-sided 95% confidence intervals (CIs) will be reported. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

9.5 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.

9.6 Assessment Time Windows

In general, it is intended that all safety and efficacy data (with some exceptions) will be summarized at each time point collected regardless of assessment time windows. Because subjects may have an early termination visit at any time or may have unscheduled visits, the following conventions will be implemented.

For all safety and efficacy data, unscheduled visits are not included in the analyses unless they are considered as baseline.

The assessment visit date or start date (e.g., AEs) will be used to calculate study day, defined as the number of days from the day of first dose. The day of first dose is considered study day 1, so study day will be computed as: (Date of Assessment Data – Date of First Dose) + 1.

In all by-visit safety assessments, end of study visits and early termination visits will be combined in order to present all data available for each subject; early termination visits will not be windowed into the nearest fitting study visit. Each subject will have one end of study visit.

For efficacy outcomes, early termination data will not be combined with end of study visit information as the timing of the outcome measure is integral to the analysis. Instead, the efficacy outcome will be windowed into the nearest study visit, where Week 1 (Day 8) visit has a ± 2-day window, and Week 2 (Day 15), Week 4 (Day 29) visits have a ± 3-day window.

10. Disposition of Subjects

Disposition will be summarized by overall and by treatment group in terms of numbers and percentage of subjects who were randomized, completed the study, and discontinued from the study. The number of subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment group and percentages will be calculated using randomized subjects as the denominator unless otherwise specified. The reasons for study discontinuation will also be summarized and will include: lack of efficacy, AE, withdrawal of consent, non-compliance, lost to follow-up, disallowed concurrent medication, Investigator decision, protocol deviation, death, and other. Subjects who complete the study through Visit 6.2 will be considered study completers.

The total number of screened subjects with the number of screen failure subjects will also be tabulated.

Subject listings of disposition will be produced for all randomized subjects, subjects who prematurely discontinued, and screen failed subjects separately. The disposition listings for all randomized subjects and for randomized subjects who discontinued prematurely will include sex/age, protocol version, and end of study information. The disposition listing of screen failed subjects will include sex/age, visit and date of screen failure, and reason for screen failure; if the primary reason for screen failure is “Eligibility Criteria Not Met,” then the criteria not met will also be listed. The subject randomization information, subject’s analysis population and inclusion criteria not met/ exclusion criteria met for screen failures will be presented in separate listings.

The number and percentage of subjects with protocol deviations will be summarized according to type of deviation: any deviation, minor deviation, major deviation, and deviations related to COVID-19 (major/minor), overall and by treatment group. Major or minor deviations will be assigned by the Sponsor. A subject listing will be provided that includes the date of each deviation and the discovery date of each deviation, if the deviation was related to COVID-19, the category and description of the deviation, whether the deviation is reportable to the Institutional Review Board, and the classification of whether the deviation was judged to be major or minor.

11. Demographic and Baseline Characteristics

11.1 Demographics

The demographic variables will include age and sex. Age (years) will be summarized, overall and by treatment group, using continuous descriptive statistics. Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

Age will also be categorized as follows: <65 years and ≥65 years. The number and percentage of subjects will be presented for age group and sex. Race will not be collected in this study; all subjects will be enrolled as Asian (Japanese). A subject listing that includes all demographic variables will be provided. The childbearing potential responses for female subjects will be presented in a separate listing.

11.2 Baseline Characteristics

Baseline characteristics will include study eye diagnosis of OHT or POAG, length of time since study eye diagnosis of OHT or POAG (weeks), prior hypotensive therapy, time on prior hypotensive therapy (weeks), study eye IOP at Screening Visit, study eye mean diurnal IOP on Qualification #2 (Day 1) Visit. Additionally, visual field mean deviation, central corneal thickness and cup to disc ratio will be summarized separately for the study eye and fellow eye.

All pretreatment variables will be included along with their respective post-treatment variables in the relevant summaries and listings. Separate listings of visual field examinations and pachymetry will be produced.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities in Japanese (MedDRA/J) Version 23.1. Medical history will be collected at Screening Visit; medical history will also be collected at Qualification Visits #1 and #2.

Non-ocular and ocular medical histories will be summarized separately using discrete summary statistics and presented by treatment group and overall at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. The SOCs will be listed in alphabetical order; PTs within a SOC will be listed in the order of descending frequency across all subjects.

A separate summary table of glaucoma history by treatment group will also be presented.

Listings of medical history will be generated separately for ocular and non-ocular data. A listing of ocular surgery/laser procedures will also be produced.

12.2 Prior and Concomitant Medications

All medications taken within 30 days prior to Screening Visit and during the study will be recorded in the eCRF. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global (B3, September 2020) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next highest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name.

Prior medications are defined as those medications listed as having been taken within 30 days prior to the start of Screening with a stop date prior to study drug administration. Concomitant medications are defined as those medications listed as having been taken (1) prior to study drug administration and continuing for any period of time following the first administration of study drug through the Week 4 (Day 29) Visit or (2) at any time following the first administration of study drug through the Week 4 (Day 29) Visit.

Prior and concomitant medications will be summarized separately for non-ocular (as distinguished in eCRF as “Non-ocular”) and ocular indications by study eye and fellow eye using the safety population. Medications will be tabulated for each treatment group and for all subjects using frequencies and percentages. Subjects may have more than one medication per ATC class. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. The ATC classes and preferred names within an ATC class will be listed in alphabetical order.

A listing of combined ocular and non-ocular prior and concomitant medications will be generated and will include the dose, route, frequency, and indication, as well as the start and stop dates of the medication, whether the medication was administered for an AE (and if yes, the AE term), and whether a medication was a prior and/or concomitant medication. A separate listing of washout medications will also be presented, and will include the medicated eye, the medication stop date, the specific medication class (Rho kinase inhibitor, prostaglandin analogue, β-adrenoceptor antagonist, adrenergic agonist, muscarinic agonist, carbonic anhydrase inhibitor, or other), and the length of washout (weeks)/washout period appropriate .

13. Treatment Exposure

13.1 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

$$\text{Extent of Exposure (days)} = (\text{Date of Last Dose} - \text{Date of First Dose}) + 1$$

Extent of treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group, using the Safety population.

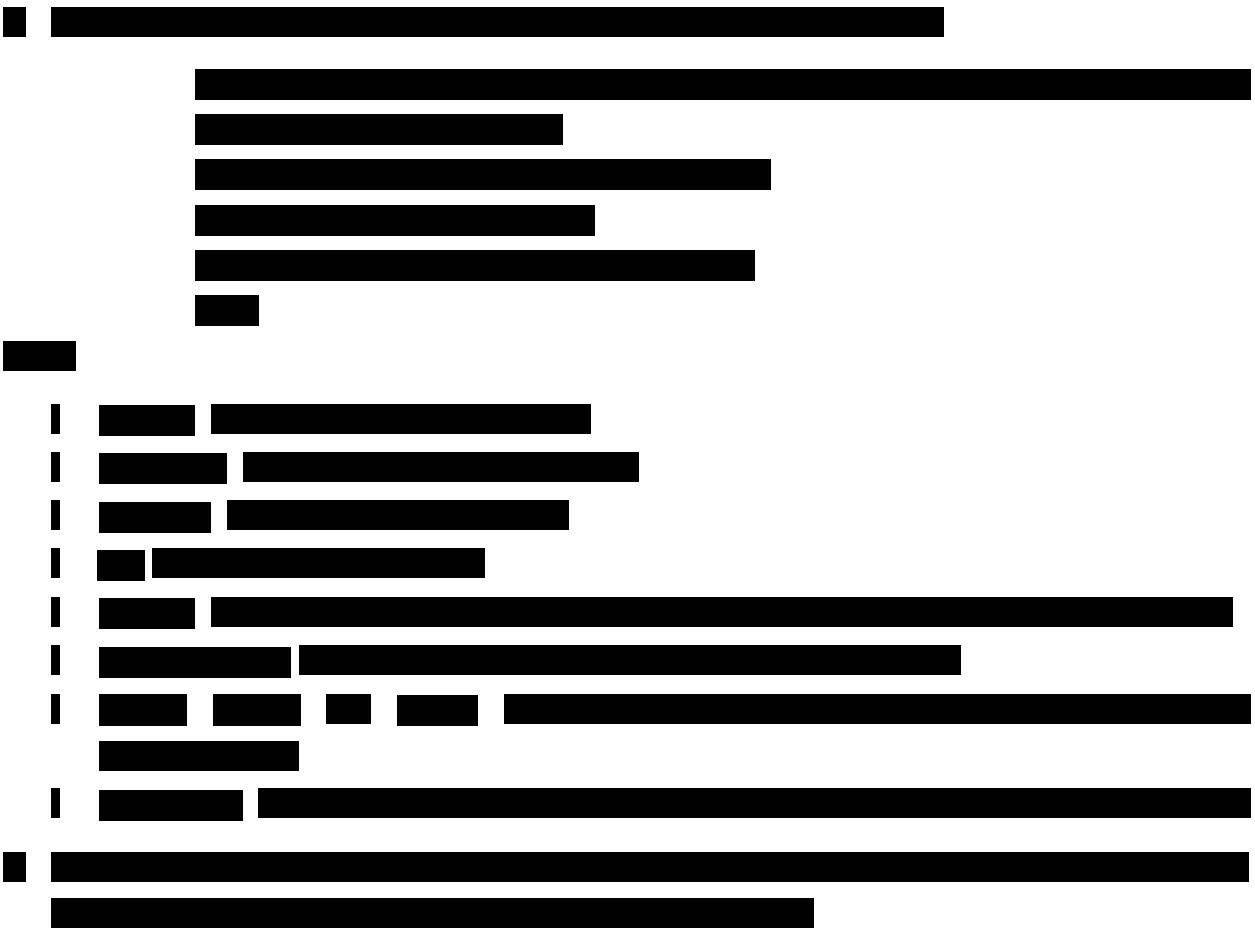
Several subject listings will be produced, including study drug administration, eye drop instillation evaluation, study medication dispensation, study medication collected, study drug eye drop, and study drug interruption.

14. Efficacy Analyses

14.1 Primary Analysis

The primary efficacy endpoint will be the mean of mean diurnal IOP at Week 4 (Day 29). The primary analysis of the primary endpoint will employ an analysis of covariance (ANCOVA) model with mean diurnal IOP at Week 4 as the response, baseline mean diurnal IOP as a covariate, and treatment as a main effect, using the ITT population with Markov Chain Monte Carlo (MCMC) and regression-based MI techniques used to impute missing data. The least squares (LS) mean difference (netarsudil QD – ripasudil BID) will be presented with a 2-sided p-value and 95% CI; if the p-value is ≤ 0.05 and the point estimate of the LS mean difference is < 0, then the netarsudil group will be considered superior to the ripasudil group.

The SAS® pseudo-code for the imputation and primary analysis is as follows, the actual code might be slightly different than the pseudo-code:



[redacted]

[redacted]

14.2 Secondary Analyses

Secondary analyses of the primary efficacy endpoint include repeating the primary analysis strategy using:

1. Observed data (ODO): For calculating the diurnal mean IOP, subjects who are missing all three IOP values at a given visit are removed from the analysis, and any observed IOP at the visit will be used to calculate the diurnal mean IOP. For example, a subject with only one IOP measurement at Week 4 will be included and the single IOP measurement will serve as the diurnal mean IOP.
2. Last observation carried forward (LOCF): Subjects who are missing any of the three IOP results at a given visit will have their worst on treatment time-consistent observation within a subject carried forward for withdrawal due to lack of efficacy or adverse event and last time-consistent observation within a subject carried forward for other missing data. For example, last observed IOP value at any 09:00 time point will be carried forward to replace a missing IOP value at 09:00 Week 4 visit if missing value is not due to AE or lack of efficacy; worst IOP value at 09:00 time point at any post-baseline visit will be carried forward to replace a missing IOP value at 09:00 time point at Week 4 visit if missing value is due to AE or lack of efficacy. Once a subject has all three IOP values at a given visit, their diurnal mean IOP at that visit will be calculated; if three values are not available for a subject, then their diurnal mean IOP will be left as missing.

In addition:

- ANCOVA with MI, LOCF, and ODO will be repeated using PP population.
- Analysis 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 and PP populations with MI, LOCF, and ODO.

Qualifying fellow eyes will be evaluated separately using ANCOVA and 2-sample t-tests with ITT population with MI.The primary and secondary analyses described above will also be completed on the following secondary endpoints:

- Mean of 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 IOP at each post-treatment time point
- Mean change from diurnally-adjusted baseline IOP at each post-treatment time point

Models adjusting for baseline will only be performed on the mean IOP response variable as that inference is identical between this response and the change from baseline IOP response variable in such a model.

Additionally, for IOP at each post-treatment time point and visit, mixed model repeated measures (MMRM) will be run using ITT ODO population . The model will include baseline time-matched IOP 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 fixed effects; and subject as a random effect. 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. An unstructured covariance matrix will be used to model between visit and time point variances within each subject. This allows for different variances and co-variances within and between time points and visits. Other covariance structures, in the order of autoregressive, Toeplitz, and compound symmetry, will be used if an unstructured covariance does not converge. The following SAS® pseudo-code using PROC MIXED will be used:

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-

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 2-sample t-tests, between netarsudil 0.02% QD and ripasudil 0.4% BID at each time point and visit, including 2-sided p-values and 95% t-distribution CIs on the difference (netarsudil - ripasudil). These analyses will be presented for ITT population with ODO.

The number and percentage of study eyes obtaining a mean diurnal IOP of ≤24 to ≤14 mmHg in 1 mmHg increments will be summarized at Week 1, Week 2, and Week 4. Analyses of IOP will also be summarized by 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. Fisher's exact test (2-sided p-values) will be used to test differences between netarsudil versus ripasudil for each category at each visit. These analyses will be presented for both the ITT and PP populations with ODO.

All primary and secondary efficacy variables, along with the corresponding planned analysis methods, are presented in Table 1 below.

Table 1. Summary of Efficacy Variables and Analysis Methods (see the next page)

Endpoints	Analysis method	population	Imputation	Tables
Mean of mean diurnal IOP at Week 4 (study eye)	ANCOVA[1]	ITT	MI	14.2.1.1.1, 14.2.1.1.3
			ODO	14.2.1.1.4
			LOCF	14.2.1.1.5
		PP	MI	14.2.1.2.1
			ODO	14.2.1.2.2
			LOCF	14.2.1.2.3
	two-sample t-tests[2]	ITT	MI	14.2.2.1.1
			ODO	14.2.2.1.2.1
			LOCF	14.2.2.1.3
		PP	MI	14.2.2.2.1
			ODO	14.2.2.2.2
			LOCF	14.2.2.2.3
Mean of mean diurnal IOP at Week 4 (fellow eye)	ANCOVA	ITT	MI	14.2.1.4
Mean of mean diurnal IOP at Weeks 1 and 2	ANCOVA	ITT	MI	14.2.1.1.2, 14.2.1.1.3
			ODO	14.2.1.1.4
			LOCF	14.2.1.1.5
		PP	MI	14.2.1.2.1
			ODO	14.2.1.2.2
			LOCF	14.2.1.2.3
	two-sample t-tests	ITT	MI	14.2.2.1.1
			ODO	14.2.2.1.2.1
			LOCF	14.2.2.1.3
		PP	MI	14.2.2.2.1
			ODO	14.2.2.2.2
			LOCF	14.2.2.2.3
Mean of mean diurnal IOP at Weeks 1 and 2 (fellow eye)	ANCOVA	ITT	MI	14.2.1.4
Mean IOP at each time point; Mean of mean diurnal IOP at each visit	ANCOVA (post-treatment)	ITT	MI	14.2.1.1.3
			ODO	14.2.1.1.4
			LOCF	14.2.1.1.5
		PP	MI	14.2.1.2.1
			ODO	14.2.1.2.2
			LOCF	14.2.1.2.3
	two-sample t-tests	ITT	MI	14.2.2.1.1
			ODO	14.2.2.1.2.1
			LOCF	14.2.2.1.3
		PP	MI	14.2.2.2.1
			ODO	14.2.2.2.2

			LOCF	14.2.2.2.3
Mean IOP at each time point; Mean of mean diurnal IOP at each visit (fellow eye)	ANCOVA (post-treatment)	ITT	MI	14.2.1.4
	two-sample t-tests	ITT	MI	14.2.2.3
Mean change from diurnally adjusted baseline IOP at each post-treatment time point	two-sample t-tests	ITT	MI	14.2.2.1.1
			ODO	14.2.2.1.2.1
			LOCF	14.2.2.1.3
		PP	MI	14.2.2.2.1
			ODO	14.2.2.2.2
			LOCF	14.2.2.2.3
Mean change from diurnally adjusted baseline IOP at each post-treatment time point (fellow eye)	two-sample t-tests	ITT	MI	14.2.2.3
Mean change from baseline in mean diurnal IOP at each post-treatment visit	two-sample t-tests	ITT	MI	14.2.2.1.1
			ODO	14.2.2.1.2.1
			LOCF	14.2.2.1.3
		PP	MI	14.2.2.2.1
			ODO	14.2.2.2.2
			LOCF	14.2.2.2.3
Mean change from baseline in mean diurnal IOP at each post-treatment visit (fellow eye)	two-sample t-tests	ITT	MI	14.2.2.3
Mean percent change from baseline in mean diurnal IOP at each post-treatment visit	two-sample t-tests	ITT	ODO	14.2.4.1
Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point	two-sample t-tests	ITT	ODO	14.2.4.1
Mean percent change from baseline in mean diurnal IOP at each post-treatment visit (fellow eye)	two-sample t-tests	ITT	ODO	14.2.4.2
Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point (fellow eye)	two-sample t-tests	ITT	ODO	14.2.4.2
Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in mean diurnal IOP levels	Fisher's exact test[3]	ITT	ODO	14.2.5.1
		PP	ODO	14.2.5.2
Mean IOP at each post-treatment visit and time point	MMRM[4]	ITT	ODO	14.2.3

[1] ANCOVA model including treatment as the main effect and baseline as the covariate. Individual models will be fit for each visit and time point.

[2] Two sample t-test comparing actual mean diurnal IOP or mean IOP value at each time point between netarsudil and ripasudil.

[3] Fisher's exact test comparing the incidence in each category at each time point between netarsudil and ripasudil.

[4] Mixed model repeated measures analysis has treatment, visit, time point, treatment*visit, treatment*time point, visit*time point, and treatment*visit*time point as fixed effects, time-matched baseline IOP as covariate, visit*time point within a subject as repeated measures, using an unstructured (or other specified) covariance matrix.

Additionally, plots of IOP measurements over time point in the ITT population (ODO) will be provided to visually assess the IOP dynamics in each treatment group:

- Line plot of mean and SE of study eye intraocular pressure (mmHg) by treatment group, visit, and time point
- Bar graph of mean (SD) of study eye mean diurnal intraocular pressure (mmHg) by treatment group and visit
- Bar graph of mean (SD) change from baseline of study eye mean diurnal intraocular pressure (mmHg) by treatment group and visit
- Bar graph of mean (SD) percent change from baseline of study eye mean diurnal intraocular pressure (mmHg) by treatment group and visit

A subject listing of IOP will also be produced.

14.3 Subgroup Analyses

Subgroup analyses of primary efficacy endpoint include the following pre-study characteristic variables. The subgroup analyses will be based on the ITT population and use ODO.

- Site
- Age: <65 years versus ≥65 years
- Sex
- Prior ocular hypotensive medication class:
    - No prior hypotensive medication
    - Prostaglandin analogues (monotherapy) only
    - Beta-adrenoceptor antagonists (monotherapy) only
    - Other monotherapy
    - Prostaglandin analogues + Beta-adrenoceptor antagonists (two drugs)
    - Other combination therapy

- Mean diurnal baseline IOP :
  - < 20 mmHg versus ≥ 20 mmHg
- Subjects with diagnosis of the study eye (POAG versus OHT)

For all subgroup analyses, mean diurnal IOP at Week 4 will be compared between treatment groups using an ANCOVA model with treatment and subgroup as the main effects, mean diurnal baseline IOP as a covariate, and the interaction of treatment and subgroup. The p-values for the subgroup and the interaction of treatment by subgroup, overall LS means, LS means by subgroup, and LS mean differences (netarsudil – ripasudil) within each subgroup category with associated p-values and 95% CIs will be presented.

Sites with fewer than five subjects will be pooled together for the analysis.

The primary efficacy ANCOVA analysis of study eye IOP at each time point and for diurnal mean will be completed for each of the mean diurnal baseline IOP categories and study eye diagnosis categories.

The secondary efficacy analysis of two-sample t-test for mean and mean change from baseline in IOP at each time point and for diurnal mean will be completed for the following: mean diurnal baseline IOP of < 20 mmHg and ≥ 20 mmHg and study eye diagnosis of POAG and OHT

15. Exploratory Analyses

There are no exploratory analyses planned for this study.

16. Safety Analyses

All safety analyses will be conducted using the Safety population.

16.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug related. The AE reporting period starts from the time the subject receives the first dose of study medication until Week 4 (Day 29). All AEs collected will be treated as TEAEs as the definition of TEAE is AE that occurs or worsens after the first dose of study medication. Documentation of AEs includes AE term, event type, eye(s), start date and time, severity, frequency, action taken with study drug, if the subject was withdrawn from the study due to the AE, other action taken, causality (relationship to study drug), outcome, stop date and time, and seriousness. All AEs will be coded using MedDRA/J (Version 23.1) SOC and PT and listed.

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 will 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

The causal relationship of the AE to study drug will be assessed by the Investigator. The following definitions will be used in assessment:

- **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.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE. This summary will also include breakdowns of TEAEs further categorized as ocular or non-ocular, TE-SAEs (treatment-emergent serious adverse events), treatment-related TEAEs (reported as possibly related or related to the study drug), treatment-related TE-SAEs, TEAEs by maximum severity, TEAEs by maximum relationship, TEAEs leading to treatment discontinuation (derived from AE CRF: "Action Taken with Study Drug" = "Investigational Product Discontinued"), TEAEs leading to study discontinuation (derived from AE CRF "Is the subject withdrawn from this study due to this AE?" = "Yes"), and TEAEs resulting in death.

Additional summaries of ocular TEAEs will be summarized using discrete summary statistics at the subject level by SOC and PT. Non-ocular TEAEs will be similarly summarized. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs and PTs within SOCs will be listed in alphabetical order.

The occurrence of ocular and non-ocular TEAEs will also be tabulated together by SOC and PT for the following:

- TE-SAEs

- Related TEAEs
- Maximum severity

Fisher's exact test will be used to test the difference in proportions of subjects with each TEAE.

Separate listings will be provided for all AEs, all SAEs, AEs leading to study drug discontinuation and AEs resulting in death.

16.2 Best-Corrected Visual Acuity

Best corrected visual acuity will be measured using Landolt-C chart or its equivalents at screening visit, Qualification #1 visit, Qualification #2 (Day 1) visit, Week 1 (Day 8) visit, Week 2 (Day 15) visit, and Week 4 (Day 29) visit.

Best corrected visual acuity observed and change from baseline results for both the study eye and the fellow eye will be summarized for each visit using the continuous summary statistics.

Separate listings of the all visual acuity results and subjects who lost three or more lines from baseline will be produced.

16.3 Biomicroscopy Examination

Biomicroscopy examination of the conjunctiva, cornea, anterior chamber, lids, iris/pupil, and lens will be performed for both eyes of subjects at every study visit and time point.

The results will be summarized using counts and percentages for each treatment group at each visit and time point for study eye and fellow eye separately. Percentages will be based on the number of subjects in each treatment group with non-missing values.

Conjunctival hyperemia will also be summarized separately by study eye and fellow eye using continuous summary statistics including mean, mean change from screening and change from baseline. Two-sample t-tests as well as Wilcoxon rank sum tests will be used to test the difference between treatment groups. The number and percentage of subjects with a clinically significant increase from baseline in conjunctival hyperemia will also be summarized in a table, the clinically significant increase is defined as +1 unit score change from baseline in either eye, with baseline defined as the maximum score prior to first dose of study medication (any time point).

A summary table of the number and percentage of subjects with at least one severity grade increase from baseline will be presented by region, parameter, visit and time point, and eye (study eye and fellow eye). Another summary table will be presented for the number and percentage of subjects with biomicroscopy finding judged to be clinically significant by the Investigator by region, parameter, visit and time point, and eye (study eye and fellow eye). Fisher's exact tests will be used to compare incidence between treatment groups in both tables. The iris/pupil region will not be analyzed in the table.

If subjects develop cornea verticillata at Week 1 (Day 8), Week 2 (Day 15), or Week 4 (Day 29), additional evaluation of grading and location (e.g. epithelium, stroma, or endothelium) of cornea verticillata will be

conducted in parallel. A separate table will be presented by parameter, visit and time point, and eye (study eye and fellow eye).

A subject listing of the biomicroscopy parameter results will be produced. A separate listing will be generated for subjects with a criterion change, defined as a +1 unit increase from baseline.

16.4 Dilated Ophthalmoscopy

A dilated funduscopic examination including evaluation of the retina, vitreous body, macula, choroid, optic nerve, and vertical cup-disc ratio will be performed at Screening and Week 4 (Day 29).

The results, including retina, macula, choroid, optic nerve, and vitreous body, will be summarized using counts and percentages for each treatment group at each visit for study eye and fellow eye. Percentages will be based on the number of subjects in each treatment group with non-missing values. A shift table of ophthalmoscopy results from baseline will also be presented by treatment group for study eye and fellow eye separately.

The vertical cup-disc ratio and change from baseline will be summarized for study eye and fellow eye separately at each visit using continuous summary statistics.

Subject listings of the dilated ophthalmoscopy results, including retina, vitreous body, macula, choroid, optic nerve and vertical cup-disc ratio, will be produced. A separate listing will be created for those subjects with a criterion change, defined as a change from “Normal” to “Abnormal” or a change from “Abnormal – Not Clinically Significant” to “Abnormal – Clinically Significant”. Additionally, a listing of subjects with increases of ≥ 0.2 from the screening vertical cup-disc ratio will be created.

16.5 Vital Signs

Vital signs, including heart rate and blood pressure, will be measured at Screening Visit, Qualification #1, Qualification #2/Day 1, Week 1 (Day 8), Week 2 (Day 15), and Week 4 (Day 29).

Vital signs will be summarized for each visit and for change from baseline to each post-treatment visit using the continuous summary statistics.

A subject listing of the vital signs results will also be produced.

16.6 Pregnancy Test

Urine pregnancy will be measured at Screening and Week 4 (Day 29) visit. A subject listing of the urine pregnancy test results will be produced.

17. Interim Analyses

No interim analysis is planned for this study.

18. Changes from Protocol-Stated Analyses

“Mean of” has been added to the primary endpoint, secondary endpoints, and hypotheses as “Mean of Mean Diurnal IOP” to differentiate mean, mean change, percent mean change in mean diurnal IOP.

19. References

None.

20. Tables

The topline tables are defined in bold.

Table Number	Title	Population
Table 14.1.1	**Subject Disposition**	
Table 14.1.2	**Demographics and Baseline Characteristics by Treatment Group**	**ITT Population**
Table 14.1.3.1	Number and Percentage of Non-Ocular Medical History	Safety Population
Table 14.1.3.2	Number and Percentage of Ocular Medical History	Safety Population
Table 14.1.3.3	Summary of Glaucoma History by Treatment Group	Safety Population
Table 14.1.4.1	Number and Percentage of Subjects with Non-Ocular Prior and Concomitant Medications	Safety Population
Table 14.1.4.2	Number and Percentage of Subjects with Ocular Prior and Concomitant Medications	Safety Population
Table 14.1.5	Exposure to Study Medication by Treatment Group	Safety Population
Table 14.2.1.1.1	**ANCOVA for Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 4**	**ITT Population (Multiple Imputations)**
Table 14.2.1.1.2	**ANCOVA for Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 1 and 2**	**ITT Population (Multiple Imputations)**
Table 14.2.1.1.3	**ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point**	**ITT Population (Multiple Imputations)**
Table 14.2.1.1.4	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (ODO)
Table 14.2.1.1.5	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (LOCF)
Table 14.2.1.2.1	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	Per-Protocol Population (Multiple Imputations)
Table 14.2.1.2.2	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) Study Eye at Each Post-Treatment Visit and Time Point	Per-Protocol Population (ODO)

Table 14.2.1.2.3	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	Per-Protocol Population (LOCF)
Table 14.2.1.3.1	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (ODO: Subjects with Mean Diurnal Baseline (Visit 3) IOP < 20 mmHg)
Table 14.2.1.3.2	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (ODO: Subjects with Mean Diurnal Baseline (Visit 3) IOP >= 20 mmHg)
Table 14.2.1.3.3	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (ODO: Subjects with Diagnosis of the Study Eye POAG)
Table 14.2.1.3.4	ANCOVA for Study Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (ODO: Subjects with Diagnosis of the Study Eye OHT)
Table 14.2.1.4	ANCOVA for Fellow Eye Intraocular Pressure (IOP; mmHg) at Each Post-Treatment Visit and Time Point	ITT Population (Multiple Imputations)
Table 14.2.2.1.1	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point**	**ITT Population (Multiple Imputations)**
Table 14.2.2.1.2.1	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point**	**ITT Population (ODO)**
Table 14.2.2.1.2.2	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point**	**ITT Population (ODO: Subjects with Mean Diurnal Baseline (Visit 3) IOP < 20 mmHg)**
Table 14.2.2.1.2.3	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point**	**ITT Population (ODO: Subjects with Mean Diurnal Baseline (Visit 3) IOP >= 20 mmHg)**
Table 14.2.2.1.2.4	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point**	**ITT Population (ODO: Subjects with POAG)**
Table 14.2.2.1.2.5	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point**	**ITT Population (ODO: Subjects with OHT)**
Table 14.2.2.1.3	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point	ITT Population (LOCF)

Table 14.2.2.2.1	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point	Per-Protocol Population (Multiple Imputations)
Table 14.2.2.2.2	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point	Per-Protocol Population (ODO)
Table 14.2.2.2.3	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit and Time Point	Per-Protocol Population (LOCF)
Table 14.2.2.3	Mean and Mean Change from Baseline in Fellow Eye Intraocular Pressure (mmHg) by Visit and Time Point	ITT Population (Multiple Imputations)
Table 14.2.3	MMRM for Study Eye Intraocular Pressure (mmHg) by Visit and Time Point	ITT Population (ODO)
Table 14.2.4.1	**Mean Percent Change from Baseline in Study Eye Intraocular Pressure (IOP; mmHg) by Visit and Time Point**	**ITT Population (ODO)**
Table 14.2.4.2	Mean Percent Change from Baseline Fellow Eye Intraocular Pressure (IOP; mmHg) by Visit and Time	ITT Population (ODO)
Table 14.2.5.1	**Categorical Summary in Study Eye Diurnal Mean Intraocular Pressure (IOP; mmHg) by Visit**	**ITT Population (ODO)**
Table 14.2.5.2	Categorical Summary in Study Eye Diurnal Mean Intraocular Pressure (IOP; mmHg) by Visit	Per-Protocol Population (ODO)
Table 14.2.6.1	ANCOVA for Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 4 by Site	ITT Population (ODO)
Table 14.2.6.2	Summary of Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 4 by Age Category (<65, >=65)	ITT Population (ODO)
Table 14.2.6.3	Summary of Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 4 by Sex	ITT Population (ODO)
Table 14.2.6.4	Summary of Mean Diurnal Intraocular Pressure (IOP; mmHg) in the Study Eye at Week 4 by Prior Ocular Hypotensive Class	ITT Population (ODO)
Table 14.2.6.5	Summary of Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 4 by Mean Diurnal Baseline IOP	ITT Population (ODO)
Table 14.2.6.6	Summary of Study Eye Mean Diurnal Intraocular Pressure (IOP; mmHg) at Week 4 by Study Eye Diagnosis	ITT Population (ODO)
Table 14.3.1.1	**Overall Summary of Treatment-Emergent Adverse Events by Treatment Group**	**Safety Population**
Table 14.3.1.2	**Number and Percentage of Subjects with Ocular Treatment-Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term**	**Safety Population**

Table 14.3.1.3	Number and Percentage of Subjects with Non-Ocular Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population
Table 14.3.1.4	Number and Percentage of Subjects with Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Treatment Group	Safety Population
Table 14.3.1.5	Number and Percentage of Subjects with Treatment-Emergent Adverse Events Related or Possibly Related to Study Medication by System Organ Class, Preferred Term, and Treatment Group	Safety Population
Table 14.3.1.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Maximum Severity, Treatment Group, System Organ Class, and Preferred Term	Safety Population
Table 14.3.2.1	Mean and Mean Change from Baseline in Study Eye Best Corrected Visual Acuity Scores by Treatment Group and Visit	Safety Population
Table 14.3.2.2	Mean and Mean Change from Baseline in Fellow Eye Best Corrected Visual Acuity Scores by Treatment Group and Visit	Safety Population
Table 14.3.3.1	**Summary of Study Eye Biomicroscopy Results by Treatment Group and Visit**	**Safety Population**
Table 14.3.3.2	Summary of Fellow Eye Biomicroscopy Results by Treatment Group and Visit	Safety Population
Table 14.3.3.3	**Mean, Mean Change from Screening, and Mean Change from Baseline in Study Eye Conjunctival Hyperemia by Treatment Group and Visit**	**Safety Population**
Table 14.3.3.4	Mean, Mean Change from Screening, and Mean Change from Baseline in Fellow Eye Conjunctival Hyperemia by Treatment Group and Visit	Safety Population
Table 14.3.3.5	Number and Percentage of Subjects with a Clinically Significant Increase from Baseline in Conjunctival Hyperemia	Safety Population
Table 14.3.3.6	Number and Percentage of Subjects with at Least One Severity Grade Increase from Baseline in Biomicroscopy Findings	Safety Population
Table 14.3.3.7	Number and Percentage of Subjects with Biomicroscopy Finding Judged to be Clinically Significant by the Investigator	Safety Population
Table 14.3.3.8	Summary of Cornea Verticillata Grading	Safety Population
Table 14.3.4.1	Summary of Study Eye Dilated Ophthalmoscopy Results by Treatment Group and Visit	Safety Population

Table 14.3.4.2	Summary of Fellow Eye Dilated Ophthalmoscopy Results by Treatment Group and Visit	Safety Population
Table 14.3.4.3	Shift Table of Study Eye Dilated Ophthalmoscopy Results by Treatment Group	Safety Population
Table 14.3.4.4	Shift Table of Fellow Eye Dilated Ophthalmoscopy Results by Treatment Group	Safety Population
Table 14.3.5.1	Mean and Mean Change from Baseline in Study Eye Vertical Cup-to-Disc Ratio by Treatment Group and Visit	Safety Population
Table 14.3.5.2	Mean and Mean Change from Baseline in Fellow Eye Vertical Cup-to-Disc Ratio by Treatment Group and Visit	Safety Population
Table 14.3.6	Mean and Mean Change from Baseline in Vital Signs by Treatment Group and Visit	Safety Population

21. Listings

Listing Number	Title	Population
Listing 16.1.7	Randomization	Randomized Population
Listing 16.2.1.1	Subject Disposition	Randomized Population
Listing 16.2.1.2	Subject Who Prematurely Discontinued	Randomized Population
Listing 16.2.1.3	Subject Disposition for Screen Failure Subjects	All Screened Subjects
Listing 16.2.2	Protocol Deviations	Randomized Population
Listing 16.2.3.1	Analysis Populations	Randomized Population
Listing 16.2.3.2	Inclusion Criteria Not Met/Exclusion Criteria Met for Screen Failures	All Screened Subjects
Listing 16.2.4.1	Demographics and Baseline Characteristics	Randomized Population
Listing 16.2.4.2	Childbearing Potential Responses for Female Subjects	Randomized Population
Listing 16.2.4.3	Medical History (Non-Ocular)	Randomized Population
Listing 16.2.4.4	Medical History (Ocular)	Randomized Population
Listing 16.2.4.5	Ocular Surgery/Laser Procedures	Randomized Population
Listing 16.2.4.6	Pachymetry: Central Corneal Thickness	Randomized Population
Listing 16.2.4.7	Visual Field Exams	Randomized Population
Listing 16.2.4.8	Prior and Concomitant Medications	Randomized Population
Listing 16.2.4.9	Washout Medications	Randomized Population
Listing 16.2.5.1	Study Drug Administration	Randomized Population
Listing 16.2.5.2	Eye-Drop Instillation Evaluation	Randomized Population
Listing 16.2.5.3	Study Medication Dispensation	Randomized Population
Listing 16.2.5.4	Study Medication Collected	Randomized Population
Listing 16.2.5.5	Study Drug Eye Drop	Randomized Population
Listing 16.2.5.6	Study Drug Interruption	Randomized Population
Listing 16.2.6	Intraocular Pressure	Randomized Population
Listing 16.2.7.1	Adverse Events	Randomized Population
Listing 16.2.7.2	Serious Adverse Events	Randomized Population
Listing 16.2.7.3	Adverse Events Leading to Study Drug Discontinuation	Randomized Population
Listing 16.2.7.4	All Adverse Events Resulting in Death	Randomized Population
Listing 16.2.8.1	Visual Acuity	Randomized Population
Listing 16.2.8.2	Visual Acuity - Subjects Who Lost Three or More Lines from Baseline	Randomized Population
Listing 16.2.9.1	Biomicroscopy	Randomized Population
Listing 16.2.9.2	Biomicroscopy - Subjects with a Criterion Change	Randomized Population
Listing 16.2.10.1	Dilated Ophthalmoscopy	Randomized Population
Listing 16.2.10.2	Dilated Ophthalmoscopy - Subjects with a Criterion Change	Randomized Population

Listing 16.2.10.3	Cup-to-Disc Ratio	Randomized Population
Listing 16.2.10.4	Cup-to-Disc Ratio - Subjects with a Clinically Significant Increase	Randomized Population
Listing 16.2.11	Vital Signs	Randomized Population
Listing 16.2.12	Urine Pregnancy Test	Randomized Population
Listing 16.2.13	Ocular Symptoms	Randomized Population

22. Figures

Figure Number	Title	Population
Figure 14.2.1	Mean +/- SE Study Eye Intraocular Pressure (mmHg) by Treatment Group, Visit, and Time Point	ITT Population (ODO)
Figure 14.2.2	Mean (SD) of Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Treatment Group and Visit	ITT Population (ODO)
Figure 14.2.3	Mean (SD) Change from Baseline of Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Treatment Group and Visit	ITT Population (ODO)
Figure 14.2.4	Mean (SD) Percent Change from Baseline of Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Treatment Group and Visit	ITT Population (ODO)