AR-13324-CS208

A Prospective, Double-Masked, Randomized, Multicenter, Placebo-Controlled, Parallel-Group Study Assessing The Safety, Ocular Hypotensive Efficacy And Optimum Dose Concentration To Be Used Clinically Of Netarsudil Ophthalmic Solution In Subjects With Open-Angle Glaucoma Or Ocular Hypertension In Japan

NCT 03844945

16 June 2020

[redacted]

[redacted]

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

Protocol Number: **AR-13324-CS208**

Version: **2.0**

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Statistical Analysis Plan Approval

Reviewed by: [redacted]

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STATISTICAL ANALYSIS PLAN

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

Sponsor: Aerie Pharmaceuticals Ireland Limited

Protocol Number: AR-13324-CS208

Author: [redacted]

Date: June 16, 2020

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Approved by: [redacted]

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Table of Contents

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BID	Bis in die (twice daily)
CRF	Case Report Form
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
IWRS	Interactive Web Response Systems
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RDC	Remote Data Capture
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol AR-13324-CS208, Amendment 2 (Rev 2) dated 01 MAR 2019.

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 (CSR).

2. Study Objectives

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

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

2.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the mean of mean diurnal intraocular pressure (IOP) at Week 4 (Day 29).

2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- 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 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

2.3 Safety Endpoints – Treatment Period

The safety endpoints include the following:

- Ocular symptoms/adverse events (AEs)
- Visual Function Questionnaire (VFQ-25) at baseline
- Best Corrected Visual Acuity (BCVA)
- Contrast Sensitivity (CS) testing at baseline
- 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 assessment will include:

- Vital signs (heart rate and blood pressure)
- Clinical laboratory evaluations (including hematology, clinical chemistry, and urinalysis)
- Pregnancy testing (for women of childbearing potential)

2.4 Safety Endpoints – Observational Period

The endpoints in the observational period include:

- VFQ-25
- BCVA
- CS testing
- Cornea verticillata grading
- Time to cornea verticillata resolution/stabilization

2.5 Statistical Hypotheses

The primary hypotheses are:

- H_{01}: The difference between study eyes treated with netarsudil 0.01% and study eyes treated with placebo (netarsudil 0.01% - placebo), in mean diurnal IOP at Week 4 is equal to 0.
- H_{11}: The difference between study eyes treated with netarsudil 0.01% and study eyes treated with placebo (netarsudil 0.01% - placebo), in mean diurnal IOP at Week 4 is not equal to 0.
- H_{02}: The difference between study eyes treated with netarsudil 0.02% and study eyes treated with placebo (netarsudil 0.02% - placebo), in mean diurnal IOP at Week 4 is equal to 0.
- H_{12}: The difference between study eyes treated with netarsudil 0.02% and study eyes treated with placebo (netarsudil 0.02% - placebo), in mean diurnal IOP at Week 4 is not equal to 0.
- H_{03}: The difference between study eyes treated with netarsudil 0.04% and study eyes treated with placebo (netarsudil 0.04% - placebo), in mean diurnal IOP at Week 4 is equal to 0.

- H_{13}: The difference between study eyes treated with netarsudil 0.04% and study eyes treated with placebo (netarsudil 0.04% - placebo), in mean diurnal IOP at Week 4 is not equal to 0.

Superiority of a netarsudil ophthalmic solution (0.01%, 0.02% and 0.04%) to placebo will be concluded if the two-sided p-value, for testing the difference (netarsudil – placebo) to 0, is < 0.05, and the point estimate of the difference (netarsudil – placebo) < 0 at Week 4 for that concentration.

3. Study Design and Procedures

3.1 General Study Design

This will be a double-masked, randomized, multicenter, placebo-controlled, parallel-group efficacy and safety trial evaluating reduction of elevated IOP with netarsudil ophthalmic solution over a 28-day treatment period. The purpose of this study is to assess the efficacy and safety of netarsudil ophthalmic solution (0.01%, 0.02%, and 0.04%) compared to placebo in subjects that are 20 years of age or older with open-angle glaucoma (OAG) or ocular hypertension (OHT) in Japan.

All study drugs will be dosed in both eyes (OU) once daily (QD) in the evening. Subjects eligible to be enrolled in this study will be those with a diagnosis of either OAG or OHT. Approximately 208 subjects will be enrolled. Subjects who agree to participate in this study and are enrolled in the study will attend a total of six 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., five days to at least six 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 including VFQ-25, BCVA, and CS testing. If deemed eligible, the subject will be enrolled at Qualification Visit #2 and assigned to placebo or 1 of 3 investagationl products (IPs) in a 1:1:1:1 ratio according to a computer-generated randomization list. Randomization will take place using Interactive Web Response Systems (IWRS) methodology and will stratify subjects by site.

Randomized subjects will dose the assigned drug in both eyes QD in the evening (between 20:00 and 22:00 hours) beginning on Day 1 and up to and including the evening prior to the final visit at Visit 6 (Week 4). Procedures conducted at each of the Study Visits 4 to 6 will include safety and efficacy measurements, including IOP assessments. At Visits 4 to 6 (Weeks 1, 2, and 4, respectively), IOP will be assessed at 09:00, 11:00, and 16:00 hours. Following completion of the Visit 6 (Week 4) study visit procedures, subjects will exit the study. For subjects who discontinue early, every possible effort will be

made to assure there is a final visit that includes all examinations listed for Visit 6.0 (Week 4) and dilated ophthalmoscopy.

For subjects who show any evidence of cornea verticillata by slit lamp examination using the grading system for amiodarone keratopathy (Orlando 1984) during the 28-day treatment period, the assigned study drug will be discontinued, all exit visit procedures (Visit 6) will be completed and subject will be followed in an observational period starting as OBS Visit 1 (Day 1) in which subjects will undergo VFQ-25, BCVA testing, CS testing and cornea verticillata grading. All subjects with cornea verticillata will return for monthly surveillance visits (OBS Visit 2, 3 and 4) where they will undergo BCVA testing and cornea verticillata grading for 3 months. If cornea verticillata persists at the 3-month time point (OBS Visit 4), subjects will return every 2 months for BCVA testing and cornea verticillata grading until resolution or stabilization. Resolution is defined as grading of zero of the cornea verticillata grading and stabilization is defined as no worsening of the cornea verticillata grading for a minimum of one year from the commencement of dosing. Once resolution or stabilization is confirmed in both eyes, the subject will undergo VFQ-25, BCVA testing, CS testing and exit the study.

[redacted]

3.2 Schedule of Visits and Assessments

The schedules of visits and assessments are provided below.

Table 3-1. Schedule of Visits and Assessments for the Treatment Period

Treatment Period

						Post Day 1 Treatment								
Day (D)/Week (W)	Screening	Qual. #1	Qual. #2 (Day 1)			W1 (Day 8±2)			W2 (Day 15±3)			W4[1] (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[2]	X													
Demography	X													
Medical/Ophthalmic History	X	X	X											
Concomitant Medications	X	X	X			X			X			X		
HR/BP	X	X	X			X			X			X		
Urine Pregnancy Test[3]	X											X		
Clinical Labs (Chem/Hem/UA)	X[4]											X		
Symptoms/AEs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25 Questionnaire			X											
BCVA	X	X	X			X			X			X		
Contrast Sensitivity			X											
IOP	X	X[6]	X[6]	X[6]	X[6]	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[7] / Pachymetry[8]	G/P													
Visual Field[9]	X													
Ophthalmoscopy (dilated)	X													X
Eye-Drop Instillation Evaluation	X													
Study Medications Dispensed					X									
Study Medications Collected												X[10]		
Study Completed														X

Abbreviations: HR/BP = heart rate/blood pressure; Chem/Hem/UA = Chemistry/Hematology/Urinalysis; AE = adverse event; IOP = Intraocular pressure.
Early Discontinuation: Visit 6.0 procedures are to be completed plus a dilated ophthalmoscopy examination.
Visit Requirements:+ IOP measurements will be 09:00 (+30 mins), 11:00 (+30 mins) and 16:00 (±30 mins) hours with the exception of the Visit 1 (Screening).

1. If subjects develop cornea verticillata at visit 4 or visit 5, study procedures for visit 6 (Exit Visit) will be completed before entering into the observational period
2. Subjects currently using ocular hypotensive medications must undergo a minimum washout period (see Section 5.7.1).
3. Urine pregnancy test for women of childbearing potential is required.
4. For subjects who are unable or unwilling to have blood drawn and urine collected for clinical labs at Visit 1 (Screening), the blood and urine sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).
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. Individuals returning at an Unscheduled Visit within 1 week to re-attempt IOP qualification are required to only re-measure IOP in both eyes.
7. Gonioscopy evaluation up to 3 months prior to randomization is acceptable.
8. Pachymetry within 1 week prior to screening is acceptable.
9. 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.
10. Collect kit(s) dispensed during the Day 1 visit.

Table 3-2. Schedule of Visits and Assessments for the Observational Period

Observational Period

Study Procedures	OBS Visit 1 (Day 1) Visit when cornea verticillata is diagnosed	OBS Visits 2-4 Monthly Visit x3 (30 ± 5 days if Cornea Verticillata Persist)	OBS Visit 5 and up Bi-monthly Visits after 3rd Monthly visit (60 ± 5 days if Cornea Verticillata Persist)	Final Visit if Resolution/ Stabilization of Cornea Verticillata [1,2] is confirmed
Discontinuation of IP	X			
Conmed Review	X	X	X	X
Symptoms/ Assessment of Ocular and General Health	X	X	X	X
VFQ-25	X			X
Best Corrected Visual Acuity	X	X	X	X
Contrast Sensitivity	X			X
Cornea Verticillata Grading	X	X	X	X

1. Should have a grading score of zero OU or stabilization confirmed to exit the study.
2. If cornea verticillata grading is zero at any visit, or stabilization of cornea verticillata is confirmed, the subject completes outlined procedures listed in Final Visit and exits the study.

4. Study Treatments

Subjects will be randomized to receive netarsudil ophthalmic solution (0.01%, 0.02%, or 0.04%) or its placebo, administered OU. Subjects will instill one drop into each eye QD in the evening between 20:00 and 22:00 hours. Study drug 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.

4.1 Method of Assigning Subjects to Treatment Groups

A randomization code for allocating the treatments will be prepared by an independent biostatistician who is not involved in the day-to-day conduct of the study. Subjects will be randomized using IWRS in a 1:1:1:1 ratio to receive netarsudil ophthalmic solution (0.01%, 0.02% or 0.04%) or its placebo and will be stratified by site.

4.2 Masking

Treatment assignments will be masked to the Investigator, the clinical study team (Sponsor, personnel involved in day to day study management, Monitors, Data Managers, and Statisticians), and the subjects for the duration of the study. Only in case of medical emergency or occurrence of AEs that warrant unmasking in the opinion of the Investigator, will the treatment assignment(s) be unmasked and made available to the Investigator and the Sponsor Medical Monitor or designee. Individual unmasking by the Investigator will normally result in withdrawal of the subject from the study and should only be performed for the specific subject requiring unmasking. In 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.

5. Sample Size and Power Considerations

Assuming a two-sided test with alpha = 0.05, a common standard deviation (SD) of 3.5 mmHg at each time point yielding a common SD of 3.0 for the diurnal mean, and a correlation among time points of 0.60, 49 intent-to-treat (ITT) subjects per arm yields at least 90% power to demonstrate superiority of netarsudil (0.01%, 0.02%, or 0.04%) to placebo in mean diurnal study eye IOP (average of 09:00, 11:00, and 16:00 hours) at the Week 4 visit assuming a difference of at least 2.0 mmHg in the mean diurnal IOP. Accounting for approximately a 5% discontinuation rate, 52 subjects per arm (208 total) will be enrolled.

6. Data Preparation

Study data will be recorded via electronic case report forms (eCRF). 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 eCRFs via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator

who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

Final analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to [redacted] standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate [redacted] 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. Analysis Populations

7.1 Intent-to-Treat Population

The ITT population will include all randomized subjects who have received at least one dose of study drug. 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.

7.2 Per Protocol Population

The per protocol (PP) population is a subset of the ITT population, which will include those subjects who do not have major protocol deviations 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.

7.3 Safety Population

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

7.4 Cornea Verticillata Safety Population

The cornea verticillata safety population will include all subjects in the safety population who develop cornea verticillata during the study. This population will be used to summarize safety variables within the observational period and will summarize subjects as treated.

8. General Statistical Considerations

8.1 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 3.0. If both eyes have the same IOP at 09:00 hours on Visit 3.0, then the right eye will be the study eye.

8.2 Missing or Inconclusive Data Handling

Any missing, unused, or spurious data will be noted in the final CSR. Analyses will be performed primarily on the ITT population with multiple imputation techniques (e.g., Monte Carlo Markov Chain [MCMC]) used to impute missing data, and secondarily using observed data only and last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures (i.e., from the same time point of the most recent visit with a non-missing value). The analyses will also be repeated on the PP population to determine the robustness of results.

8.3 Definition of Baseline

For diurnally-adjusted IOP, baseline will refer to the time-relevant measure at Visit 3 (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; etc.). For all other variables, baseline is defined as the last measurement prior to the first dose of study drug. 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.

8.4 Data Analysis Conventions

All data analysis will be performed by [redacted] 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. All study data will be listed by subject, treatment, and visit / time point (as applicable) based on all randomized subjects unless otherwise specified.

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 frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CIs) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four 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.”

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit / time point.

8.5 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 (Visit 3). The day of first dose (Visit 3) is considered study day 1, so study day will be computed as: (Date of Assessment Data – Date of Visit 3) + 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 Visit 4 has a ± 2 day window, and Visit 5 and Visit 6 have a ± 3 day window.

8.6 Adjustments for Multiplicity

There will be no adjustment for the multiplicity of these active concentrations (0.01%, 0.02%, or 0.04%) tested against placebo in this Phase 2 study.

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages 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 and percentages will be calculated using randomized subjects as the denominator. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects. Subject listings of disposition will be produced for all randomized and screen failed subjects separately.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation that will be summarized include: AE, withdrawal of consent, non-compliance,

lost to follow-up, lack of efficacy, disallowed concurrent medication, investigator decision, protocol violation, death, and an “other” category for reasons other than those previously listed. Each subject will have the single, primary reason for study discontinuation captured and summarized. The denominator for calculating the percent of subjects discontinuing the study for each reason will be the total number of discontinued subjects in the treatment group.

The number and percentage of subjects with protocol deviations (any deviations, major deviations, and minor deviations) will be summarized by treatment group for all randomized subjects. A subject listing will be provided that includes the date of the deviation, the deviation description, the deviation code, the classification of whether the deviation was judged to be major or minor, and whether the subject is included in the PP population. A separate listing for inclusion not met/exclusion met for screen failures will also be produced.

10. Demographic and Pretreatment Variables

10.1 Demographic and Baseline Characteristics Variables

Demographic and baseline characterisitics will be summarized by treatment group for the ITT population. The demographic variables will include age and sex.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. 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

Baseline characteristics will include study eye diagnosis of OHT or OAG, length of time since study eye diagnosis of OHT or OAG (weeks), prior hypotensive therapy, time on prior hypotensive therapy (weeks), study eye IOP at screening visit (Visit 1), and study eye mean diurnal IOP on Day 1 (Visit 3). Additionally, visual field mean deviation, central corneal thickness, and cup-to-disc ratio at screening visit will be summarized separately for study eye and fellow eye.

Test of differences between each of the active treatment group and placebo will be performed for demographic and baseline characteristics variables. Analysis of variance (ANOVA) will be employed to assess differences between treatments for continuous variables. Fisher’s exact test will be used to assess differences between treatments for categorical variables.

A subject listing that includes all demographic and baseline characteristics variables will be provided. Separate listings of childbearing potential responses for female subjects, visual field exams, central corneal thickness will also be produced.

10.2 Pretreatment Variables

All pretreatment variables will be included along with their respective post-treatment variables in the relevant summaries and listings.

10.3 Visual Function Questionnaire (VFQ-25)

The VFQ-25 is a reliable and valid 25-item version of the 51-item National Eye Institute Visual Function Questionnaire that measures subjective assessment of patient-reported vision-targeted health status elements that are most important to people with eye disease. All subjects will undergo VFQ-25 at Visit 3 (Qualification #2, Day 1, 09:00) in the treatment period. For observational period, the VFQ-25 data will be collected at OBS Visit 1 and Final Visit.

The VFQ-25 sub-scale scores and composite score will be calculated as the steps below.

Table 15-1 Step 1: Recoding of Items

Question Numbers	Original Item Score[(a)]	Recoded Value
1, 3, 4, 15c[(b)]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a, A3, A4, A5, A6, A7, A8, A9	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17, 18, 19, 20, 21, 22, 23, 24, 25, A11a, A11b, A12, A13	1	0
	2	25
	3	50
	4	75
	5	100
A1, A2	0 to 10	0 to 10

[(a)]Precoded response choices as printed in the questionnaire.
[(b)]Question 15c has four-response level, but is expended to a five-levels using question 15b.
Note: If 15b=1 then 15c should be recoded to 0.
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.
*Response choice “6” indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as “missing”.

Table 15-2 Step 2: Averaging Items to Generate VFQ-25 Sub-Scales

Sub-Scale	Number of items	Items to be averaged (after recoding per Table 15-1)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

The subject's sub-scale score is the average of scores from non-missing items. The higher scores indicate better vision-specific health-related quality of life. The subject's composite VFQ-25 score is the average of all sub-scale scores except for the general health item.

The VFQ-25 sub-scale scores and composite score will be summarized using the continuous summary statistics for Visit 3.

A subject listing of VFQ-25 sub-scale and composite scores will also be produced.

10.4 Contrast Sensitivity Testing

Contrast sensitivity charts will be used to assess visual function. All subjects will have a CS testing at Visit 3 in the treatment period. In the observational period, the CS data will be collected at OBS Visit 1 and Final Visit.

The CS results will be summarized at eye level using the discrete summary statistics for each spatial frequency by treatment group. The numeric part of the CS results will be summarized using continuous summary statistics.

A subject listing of CS testing will also be produced.

11. Medical History and Concomitant Medications

11.1 Medical History

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, must be recorded. Medical history will be coded using the Medical Dictionary for Regulatory Activities in Japanese (MedDRA/J), Version 21.1.

Ocular and non-ocular medical history will be summarized separately using discrete summary statistics by treatment group 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.

Additionally, glaucoma history will be summarized similary to ocular history.

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

11.2 Prior and Concomitant Medications

Use of all medications will be documented on the appropriate CRF. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Global, B3, September 2018) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest 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 (eg, multivitamins) then the drug name will be summarized as the preferred name.

Concomitant medications will be summarized separately for ocular and non-ocular data using the safety population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications.

Listings of prior and concomitant medications will be generated separately for ocular and non-ocular data. Listing of washout medication will also be produced.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Dosing compliance is calculated as: 100 * (Number of Actual Dosing Days) / (Number of Expected Dosing Days). Dosing compliance will be summarized with continuous descriptive statistics for each treatment group, using the safety population.

12.2 Treatment Exposure

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

Extent of Exposure (days) = (Date of Last Dose – Date of Visit 3) + 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.

A subject listing of study drug administration will also be produced.

13. Efficacy Analyses

13.1 Primary Efficacy 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 of mean diurnal IOP at Week 4 as the response, baseline mean of mean diurnal IOP as a covariate, and treatment as a main effect, using the ITT population with MCMC multiple imputation techniques used to impute missing data. The least squares (LS) mean differences (netarsudil – placebo) will be presented separately for netarsudil 0.01%, 0.02%, and 0.04% as well as two-sided p-values and 95% CIs. For a given comparison, 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 placebo.

The following SAS code will be used for multiple imputations using the MCMC method:

```
proc mi data = indata seed = 48669 out = outdata1;
  mcmc initial = em;
  var trt01pn baseline IOP;
run;
```

where

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

Five (5) complete data sets will be generated from the above code. Each complete data set will be used to analyze this primary efficacy endpoint separately using ANCOVA. Then, the SAS procedure MIANALYZE will be used to analyze the results from the 5 complete data sets to generate a combined inference. The following SAS code will be used:

```
ods output diffs = outdata2;
proc mixed data = outdata1;
  class trt01pn;
  model IOP = trt01pn baseline;
  lsmeans trt01pn / cl pdiff;
```

```
  by _Imputation_;
run;
proc sort data = outdata2;
  by trt01pn _trt01pn;
run;
ods output ParameterEstimates = outdata3;
proc mianalyze data = outdata2 alpha = 0.05;
   by trt01pn _trt01pn;
   modeleffects estimate;
   stderr stderr;
run;
```

where

- *IOP* is the name of the IOP measure
- *trt01pn* is the name of the treatment group variable in numeric format
- *outdata2* is the name of the output dataset that contains the statistical results of the differences between treatment groups
- *outdata3* is the name of the output dataset that contains summary and inferential statistics.

13.2 Secondary Efficacy Analyses

Secondary analyses of the primary efficacy endpoint include repeating the primary analysis strategy using observed data only, and LOCF where LOCF will be performed using time-relevant measures. These analyses will also be repeated on the PP population to determine robustness of results.

Additionally, secondary analyses of the primary endpoint will be completed using the two-sample t-test and 95% t-distribution CIs on the difference (netarsudil (0.01%, 0.02%, and 0.04%) - placebo) for each comparion.

The secondary efficacy endpoints include:

- 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 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

Similar ANCOVA models for primary efficacy endpoint will be used for mean of mean diurnal IOP at Weeks 1 and 2, and mean IOP at each post-treatment time point (09:00, 11:00, and 16:00 at the Week 1, Week 2, and Week 4 Visits).

Additionally, for IOP at each post-treatment time point, mixed model repeated measures (MMRM) will be run with 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 repeated measure, using an unstructured covariance matrix. The LS mean differences (netarsudil – placebo) will be presented separately for netarsudil 0.01%, 0.02%, and 0.04% as well as two-sided p-values and 95% CIs. This analysis will be performed for the ITT population with observed data only.

Two-sample t-test and 95% t-distribution confidence intervals on the difference (netarsudil [0.01%, 0.02%, and 0.04%] - placebo) will be used for mean change from baseline in mean diurnal IOP at each post-treatment visit, mean change from diurnally-adjusted baseline IOP at each post-treatment time point, mean percent change from baseline in mean diurnal IOP at each post-treatment visit, and mean percent change from diurnally-adjusted baseline IOP at each post-treatment time point.

The number and percentage of study eyes obtaining a mean diurnal IOP of ≤22 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 ≥4 to ≥12 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 (two-sided p-values) will be used to test differences between netarsudil (0.01, 0.02%, or 0.04%) versus placebo for each category at each visit. These analyses will be presented for both the ITT and PP populations with observed data only.

All primary and secondary efficacy variables, along with the corresponding planned analysis methods, are presented in Table 13-1.

Table 13-1. Summary of Efficacy Variables and Analysis Methods

	Two Sample t-test[a]	ANCOVA[b]	MMRM[c]	Fisher's Exact Test[d]	Analysis Population	Missing Data Imputation
Primary Analysis						
Mean of Mean diurnal IOP at Week 4		X			ITT	MCMC
Secondary Analyses						
Mean of Mean diurnal IOP at Week 4	X	X			ITT	MCMC, LOCF, Observed Data
Mean of Mean diurnal IOP at Week 1 and Week 2	X	X			ITT	MCMC, LOCF, Observed Data
Mean diurnal IOP at Week 1, Week 2 and Week 4	X	X			PP	MCMC, LOCF, Observed Data
Mean change from baseline in mean diurnal IOP at each post-treatment visit	X				ITT,PP	MCMC, LOCF, Observed Data
Mean percent change from baseline in mean diurnal IOP at each post-treatment visit	X				ITT	Observed Data
Mean IOP at each post-treatment time point	X	X			ITT, PP	MCMC, LOCF, Observed Data
Mean IOP at each post-treatment visit			X		ITT	Observed Data
Mean change from diurnally adjusted baseline IOP at each post-treatment time point	X				ITT, PP	MCMC, LOCF, Observed Data
Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point	X				ITT	Observed data
Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels				X	ITT, PP	Observed data

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

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

[c] 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 covariance matrix.

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

Additionally, mean IOP with standard error (SE) will be displayed graphically. A Subject Listing of IOP will also be produced.

13.3 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 observed data only.

- Site
- Age: <65 years versus ≥65 years
- Sex
- Prior hypotensive medication experience category 1: Combination Therapy, Prostaglandin (monotherapy), Other (monotherapy), No Prior Therapy
- Prior hypotensive medication experience category 2: Prior Prostaglandin, No Prior Prostaglandin
- Maximum baseline IOP value: <17 mmHg, <19 mmHg , <21 mmHg, <23 mmHg, <25 mmHg , <27 mmHg, <30 mmHg, <32 mmHg

For all subgroup analyses, except maximum baseline IOP value, 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 LS mean differences (netarsudil – placebo), p-values for testing the treatment difference, and the interaction of treatment by subgroup will be presented.

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

The primary efficacy analysis of mean diurnal IOP at Week 4 will be completed for maximum baseline IOP <17 mmHg, <19 mmHg , <21 mmHg, <23 mmHg, < 25 mmHg, <27 mmHg, <30 mmHg, <32 mmHg, and <35 mmHG

The secondary efficacy analysis of two-sample t-test for mean and mean change from baseline in IOP at each timeline and for diurnal mean will be completed for maximum baseline IOP <17 mmHg, <19 mmHg , <21 mmHg, <23 mmHg, < 25 mmHg, <27 mmHg, <30 mmHg, <32 mmHg, and <35 mmHG.

Additional post-hoc analyses were performed for IOP of subjects with prior hypotensive therapy and subjets with no prior therapy.

14. Exploratory Analyses

There are no exploratory analyses planned for this study.

15. Safety Analyses – Treatment Period

All safety analyses will be conducted using the safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF. AEs should be

documented from the time the subject receives the first dose of study drug until 30 days after the last dose of study drug.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated, and by study completion date.

Adverse events are coded using the MedDRA/J, Version 21.1. An overall summary will be presented to report the number of events and incidents of subjects having at least one event in the following categories:

- TEAEs
- Ocular TEAEs
- Non-ocular TEAEs
- Serious TEAEs
- Treatment-related TEAEs (reported as possibly related or related to the study drug)
- Treatment-related serious TEAEs
- TEAEs by maximum severity
- TEAEs leading to study drug discontinuation
- TEAEs resulting in death

Separate summaries will be provided for the number and percentage of TEAEs by SOC and PT for the following categories as well as the p-values for comparing the incidence between each netarsudil (0.01%, 0.02%, and 0.04%) group and placebo:

- Ocular TEAEs
- Non-ocular TEAEs
- Serious TEAEs
- Treatment-related TEAEs (reported as possibly related or related to the study drug)

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 summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency within each SOC.

Treatment-emergent AEs will also be summarized by SOC, PT, and maximum severity. If a subject experiences more than one AE within SOC or PT, that subject will be counted only once for that event under the maximum severity.

All AEs will be presented in a subject listing. In addition, all serious AEs and AEs leading to study drug discontinuation will be listed separately.

15.2 Best Corrected Visual Acuity

Best corrected visual acuity will be measured using Landolt-C chart or its equivalents at Visit 1, Visit 2, Visit 3.0, Visit 4.0, Visit 5.0, and Visit 6.0.

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.

A subject listing of the BCVA results will be produced.

15.3 Biomicroscopy Examination

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

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

A summary table of the number and percentage of subjects with at least one severity grade increase from baseline will be presented by region, finding, visit, 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, finding, visit 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. Note: iris/pupil will not be analyzed in the table.

Additionally, Conjunctival hyperemia will also be summarized using continuous summary statistics including change from baseline and change from Visit 1. Two-sample t-tests as well as Wilcoxon rank sum tests will be used to test the difference between treatment groups.

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.

15.4 Dilated Ophthalmoscopy

A dilated funduscopic examination including evaluation of the retina, vitreous, macula, choroid, optic nerve, and vertical cup/disc ratio will be performed at Visit 1 and Visit 6.2.

The results including retina, vitreous, macula, choroid, and optic nerve 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-to-disc ratio will be summarized for study eye and fellow eye at each visit and change from baseline to each visit using continuous summary statistics.

Subject listings of the dilated ophthalmoscopy results (one listing for retina, vitreous, macula, choroid, and optic nerve, one listing for vertical cup-to-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-to-disc ratio will be created.

15.5 Vital Signs

Vital signs, including heart rate and blood pressure, will be measured at Visit 1, Visit 2, Visit 3.0, Visit 4.0, Visit 5.0, and Visit 6.0.

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.

15.6 Clinical Laboratory Data

Clinical laboratory data including clinical chemistry, hematology, and urinalysis will be collected at Visit 1 or Visit 2 (if not performed at Visit 1), and Visit 6.0.

Quantitative clinical laboratory results will be summarized for each visit and for change from baseline to Visit 6.0 using continuous summary statistics. Qualitative clinical laboratory results will be summarized using discrete summary statistics. Shifts from baseline to Visit 6.0 will also be presented using discrete summary statistics. Additionally, number and percentage of subjects with any abnormal values in clinical chemistry and hematology will be summarized by treatment group.

Clinical laboratory results, including clinical chemistry, hematology, and urinalysis/urine microscopic, will be presented in data listings. Abnormal results, those above or below the normal range, will be flagged with “H” (high), “HP” (high panic), “L” (low), “LP” (low panic), or “AB” (abnormal) based on the laboratory ranges provided by the lab and included in the listings.

16. Safety Analyses – Observational Period

Cornea verticillata safety population will be used in the analyses for observational period.

Listings of subject disposition, demographics and baseline characteristics, and AEs (all AEs, serious AEs, AEs resulting in study drug discontinuation) will be produced. Summary of subject disposition, demographics and baseline characteristics, and TEAEs will be summarized similarly to those for treatment period.

16.1 Visual Function Questionnaire

The subjects who develop cornea verticillata will undergo VFQ-25 at OBS Visit 1 (when cornea verticillata is diagnosed) and the final visit. The scores and the score changes from OBS Visit 1 will be summarized using the continuous summary statistics by treatment group.

16.2 Best Corrected Visual Acuity

Best Corrected Visual Acuity will be taken at all visits during the observational period. Best correct visual acuity collected during the observation period will be summarized similarly to that of treatment period.

16.3 Contrast Sensitivity Testing

The CS testing will undergo at OBS Visit 1 (when cornea verticillata is diagnosed) and the final visit. The CS results will be summarized at eye level using discrete summary statistics for each spatial frequency by treatment group, and by whether or not the corneal verticillata deposit event is ongoing at given visit. The numeric part of the CS results will be summarized at eye level using the continuous summary statistics.

16.4 Cornea Verticillata Grading

Subjects who are diagnosed with cornea verticillata by slit lamp examination will undergo grading of the corneal deposits using a published grading scale for amiodarone-induced cornea verticillata. The corneal deposits will be graded at all visits during the observational period. The scores and the score changes from Visit 1 will be summarized at eye level using continuous summary statistics by treatment group, and by whether or not the cornea verticillata deposit event is ongoing at given visit.

16.5 Time to Cornea Verticillata Resolution/Stabilization

Resolution of cornea verticillata is defined as a cornea verticillata deposit grade of zero. Stabilization is defined as no worsening of the cornea verticillata grading for a minimum of one year from the commencement of dosing. The time to cornea verticillata resolution/stabilization will be evaluated in days related to start date of cornea verticillata at the eye level. Kaplan-Meier methods will be used to estimate median time to cornea verticillata resolution/stabilization, as well as the 25th and 75th percentiles by treatment group and overall netarsudil-treated subjects. Associated 95% CIs will also be

estimated. Kaplan-Meier curves will also be presented by treatment group and overall netarsudil treated subjects.

17. Interim Analyses

No interim analysis is planned for this study.

18. Changes from Protocol-Stated Analyses

In the protocol AR-13324-CS208, Amendment 2, it states "Superiority for a concentration (0.01%, 0.02% and 0.04%) will be concluded if the 2-sided p-value, for testing the difference (netarsudil – placebo) to 0, ≤ 0.05 and the point estimate of the difference < 0 at Week 4 for that concentration" on page 61-62 of 86. The SAP changes ≤ 0.05 to <0.05 for the 2-sided p-value.

19. References

US Federal Register. (1998) International Conference on Harmonization; Guidance for Industry: Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration. Federal Register, Vol. 63, No. 179, September 16, 1998, page 49583. (E9)

US Federal Register. (1996) International Conference on Harmonization; Guidance for Industry: Structure and Content of Clinical Study Reports. Department of Health and Human Services: Food and Drug Administration. Federal Register Vol. 61, July 17, 1996, page 37320. (E3)

20. Revision History

Section #	Description of Change
13.3	Subgroup analysis of primary analysis for <35 mmHG and subgroup analysis of sencondary analysis is added. These analyses were conducted as a priori analyses, however were missing in SAP version 1.0 due to overshight.
21,22, 23	Added

21. Tables

Post-hoc tables are indicated in bold font.

Table Number	Title	Population
14.1.1	Subject Disposition	Randomized Subjects
14.1.2	Demographics and Baseline Characteristics by Treatment Group	Intent-to-Treat Population
14.1.3.1	Number and Percentage of Subjects with Non-Ocular Medical History	Safety Population
14.1.3.2	Number and Percentage of Subjects with Ocular Medical History	Safety Population
14.1.3.3	Summary of Glaucoma History by Treatment Group	Safety Population

14.1.3.4	Summary of Visual Function Questionnaire (VFQ-25) Results at Baseline	Safety Population
14.1.3.5	Summary of Contrast Sensitivity Testing in Study Eye at Baseline	Safety Population
14.1.3.6	Summary of Contrast Sensitivity Testing in Fellow Eye at Baseline	Safety Population
14.1.4.1	Number and Percentage of Subjects with Non-Ocular Prior and Concomitant Medications	Safety Population
14.1.4.2	Number and Percentage of Subjects with Ocular Prior and Concomitant Medications	Safety Population
14.1.5	Exposure to Study Medication by Treatment Group	Safety Population
14.2.1.1.1	ANCOVA for Study Eye Mean Diurnal Intraocular Pressure (mmHg) at Week 4 – MCMC Multiple Imputations	Intent-to-Treat Population
14.2.1.1.2	ANCOVA for Study Eye Mean Diurnal Intraocular Pressure (mmHg) at Weeks 1 and 2 – MCMC Multiple Imputations	Intent-to-Treat Population
14.2.1.1.3	ANCOVA for Study Eye Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – MCMC Multiple Imputations	Intent-to-Treat Population
14.2.1.1.4	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population
14.2.1.1.5	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – LOCF	Intent-to-Treat Population
14.2.1.2.1	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – MCMC Multiple Imputations	Per Protocol Population
14.2.1.2.2	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Per Protocol Population
14.2.1.2.3	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – LOCF	Per Protocol Population
14.2.1.3.1	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 17 mmHg)
14.2.1.3.2	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 19 mmHg)
14.2.1.3.3	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 21 mmHg)

14.2.1.3.4	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 23 mmHg)
14.2.1.3.5	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 25 mmHg)
14.2.1.3.6	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 27 mmHg)
14.2.1.3.7	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 30 mmHg)
14.2.1.3.8	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 32 mmHg)
14.2.1.3.9	ANCOVA for Study Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 35 mmHg)
14.2.1.4	ANCOVA for Fellow Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point – MCMC Multiple Imputations	Intent-to-Treat Population
14.2.2.1.1	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – MCMC Multiple Imputations	Intent-to-Treat Population
14.2.2.1.2	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population
14.2.2.1.2.1	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 17 mmHg)
14.2.2.1.2.2	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 19 mmHg)
14.2.2.1.2.3	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 21 mmHg)
14.2.2.1.2.4	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 23 mmHg)
14.2.2.1.2.5	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 25 mmHg)
14.2.2.1.2.6	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 27 mmHg)

14.2.2.1.2.7	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 30 mmHg)
14.2.2.1.2.8	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 32 mmHg)
14.2.2.1.2.9	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Intent-to-Treat Population (Subjects with Maximum Baseline IOP < 35 mmHg)
14.2.2.1.2.10	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data**	**Intent-to-Treat Population (Subjects with Prior Hypotensive Therapy)**
14.2.2.1.2.11	**Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data**	**Intent-to-Treat Population (Subjects with No Prior Therapy)**
14.2.2.1.3	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – LOCF	Intent-to-Treat Population
14.2.2.2.1	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – MCMC Multiple Imputations	Per Protocol Population
14.2.2.2.2	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – Observed Data	Per Protocol Population
14.2.2.2.3	Mean and Mean Change from Baseline in Study Eye Intraocular Pressure (mmHg) by Visit – LOCF	Per Protocol Population
14.2.2.3	Mean and Mean Change from Baseline in Fellow Eye Mean Intraocular Pressure (mmHg) by Visit – MCMC Multiple Imputations	Intent-to-Treat Population
14.2.3	MMRM for Study Eye Intraocular Pressure (mmHg) – Observed Data	Intent-to-Treat Population
14.2.4.1	Mean Percent Change from Baseline in Study Eye Intraocular Pressure (mmHg) at Each Post-Treatment Time Point - Observed Data	Intent-to-Treat Population
14.2.4.2	Mean Percent Change from Baseline in Fellow Eye Mean Intraocular Pressure (mmHg) at Each Post-Treatment Time Point - Observed Data	Intent-to-Treat Population
14.2.5.1	Categorical Summary in Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Visit - Observed Data	Intent-to-Treat Population
14.2.5.2	Categorical Summary in Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Visit - Observed Data	Per Protocol Population
14.2.6.1	ANCOVA for Study Eye Mean Diurnal IOP at Week 4 by Subgroup of Site - Observed Data	Intent-to-Treat Population
14.2.6.2	ANCOVA for Study Eye Mean Diurnal IOP at Week 4 by Subgroup of Age Category (<65 Years vs ≥65 Years) - Observed Data	Intent-to-Treat Population
14.2.6.3	ANCOVA for Study Eye Mean Diurnal IOP at Week 4 by Subgroup of Sex - Observed Data	Intent-to-Treat Population

14.2.6.4	ANCOVA for Study Eye Mean Diurnal IOP at Week 4 by Subgroup of Prior Hypotensive Medication Category 1 - Observed Data	Intent-to-Treat Population
14.2.6.5	ANCOVA for Study Eye Mean Diurnal IOP at Week 4 Prior Hypotensive Medication Category 2 - Observed Data	Intent-to-Treat Population
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events by Treatment Group	Safety Population
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
14.3.1.3	Number and Percentage of Subjects with Non-Ocular Treatment-Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term	Safety Population
14.3.1.4	Number and Percentage of Subjects with Serious Treatment-Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term	Safety Population
14.3.1.5	Number and Percentage of Subjects with Treatment-Related Treatment-Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term	Safety Population
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
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
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
14.3.3.1	Summary of Study Eye Biomicroscopy Results by Treatment Group and Visit	Safety Population
14.3.3.2	Summary of Fellow Eye Biomicroscopy Results by Treatment Group and Visit	Safety Population
14.3.3.3	Mean, Mean Change from Visit 1, and Mean Change from Baseline in Study Eye Conjunctival Hyperemia by Treatment Group and Visit	Safety Population
14.3.3.4	Mean, Mean Change from Visit 1, and Mean Change from Baseline in Fellow Eye Conjunctival Hyperemia by Treatment Group and Visit	Safety Population
14.3.3.5	Number and Percentage of Subjects with a Clinically Significant Increase from Baseline in Conjunctival Hyperemia	Safety Population

14.3.3.6	Number and Percentage of Subjects with at Least One Severity Grade Increase from Baseline in Biomicroscopy Findings	Safety Population
14.3.3.7	Number and Percentage of Subjects with Biomicroscopy Findings Judged Clinically Significant by the Investigator	Safety Population
14.3.4.1	Summary of Study Eye Dilated Ophthalmoscopy Results by Treatment Group and Visit	Safety Population
14.3.4.2	Summary of Fellow Eye Dilated Ophthalmoscopy Results by Treatment Group and Visit	Safety Population
14.3.4.3	Shift Table of Study Eye Dilated Ophthalmoscopy Results by Treatment Group	Safety Population
14.3.4.4	Shift Table of Fellow Eye Dilated Ophthalmoscopy Results by Treatment Group	Safety Population
14.3.4.5	Mean and Mean Change from Baseline in Study Eye Vertical Cup-to-Disc Ratio by Treatment Group and Visit	Safety Population
14.3.4.6	Mean and Mean Change from Baseline in Fellow Eye Vertical Cup-to-Disc Ratio by Treatment Group and Visit	Safety Population
14.3.5	Mean and Mean Change from Baseline in Vital Signs by Treatment Group and Visit	Safety Population
14.3.6.1	Mean and Mean Change from Baseline in Clinical Chemistry Values by Treatment Group and Visit	Safety Population
14.3.6.2	Mean and Mean Change from Baseline in Hematology Values by Treatment Group and Visit	Safety Population
14.3.6.3	Mean and Mean Change from Baseline in Urinalysis and Urine Microscopic Values by Treatment Group and Visit	Safety Population
14.3.6.4	Number and Percentage of Subjects with Any Abnormal Clinical Chemistry Values at End of Study by Treatment Group	Safety Population
14.3.6.5	Number and Percentage of Subjects with Any Abnormal Hematology Values at End of Study by Treatment Group	Safety Population
14.3.6.6	Summary of Clinical Chemistry Values: Shift from Baseline by Treatment Group	Safety Population
14.3.6.7	Summary of Hematology Values: Shift from Baseline by Treatment Group	Safety Population
14.3.6.8	Summary of Urinalysis and Urine Microscopic Values: Shift from Baseline by Treatment Group	Safety Population
14.3.6.9	Summary of Urinalysis and Urine Microscopic Categorical Values by Treatment Group and Visit	Safety Population
14.4.1	Subject Disposition Cornea Verticillata	Safety Population

14.4.2	Demographics and Baseline Characteristics by Treatment Group Cornea Verticillata	Safety Population
14.4.3.1	Number and Percentage of Subjects with Ocular Treatment-Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term Cornea Verticillata	Safety Population
14.4.3.2	Number and Percentage of Subjects with Non-Ocular Treatment-Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term Cornea Verticillata	Safety Population
14.4.4	Mean and Mean Change from Visit 1 in Visual Function Questionnaire (VFQ-25) Results by Treatment Group Cornea Verticillata	Safety Population
14.4.5.1	Mean, Mean Change from Baseline, and Mean Change from OBS Visit 1 in Study Eye Best Corrected Visual Acuity Results by Treatment Group Cornea Verticillata	Safety Population
14.4.5.2	Mean, Mean Change from Baseline, and Mean Change from OBS Visit 1 in Fellow Eye Best Corrected Visual Acuity Results by Treatment Group Cornea Verticillata	Safety Population
14.4.6.1	Summary of Contrast Sensitivity Testing in Study Eye by Treatment Group, and Visit Cornea Verticillata	Safety Population
14.4.6.2	Summary of Contrast Sensitivity Testing in Fellow Eye by Treatment Group, and Visit Cornea Verticillata	Safety Population
14.4.7.1	Mean and Mean Change from OBS Visit 1 in Study Eye Cornea Verticillata Grading by Treatment Group Cornea Verticillata	Safety Population
14.4.7.2	Mean and Mean Change from OBS Visit 1 in Fellow Eye Cornea Verticillata Grading by Treatment Group Cornea Verticillata	Safety Population
14.4.7.3	Time to Cornea Verticillata Resolution/Stabilization in Study Eye by Treatment Group and Overall Netarsudil-Treated Subjects Cornea Verticillata	Safety Population
14.4.7.4	Time to Cornea Verticillata Resolution/Stabilization in Fellow Eye by Treatment Group and Overall Netarsudil-Treated Subjects Cornea Verticillata	Safety Population

22. Listings

Listing Number	Title
16.1.7	Randomization Schedule
16.2.1.1	Subject Disposition
16.2.1.2	Subject Who Prematurely Discontinued
16.2.1.3	Subject Disposition for Screen Failure Subjects

16.2.2	Protocol Deviations
16.2.3.1	Analysis Populations Information
16.2.3.2	Inclusion Criteria Not Met/Exclusion Criteria Met for Screen Failures
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2	Childbearing Potential Responses for Female Subjects
16.2.4.3	Medical History (Non-Ocular)
16.2.4.4	Medical History (Ocular)
16.2.4.5	Ocular Surgery/Laser Procedures
16.2.4.6	Central Corneal Thickness
16.2.4.7	Visual Field Exams
16.2.4.8	Prior and Concomitant Medications
16.2.4.9	Washout Medications
16.2.5	Study Drug Administration
16.2.6	Intraocular Pressure (IOP)
16.2.7.1	Adverse Events
16.2.7.2	Serious Adverse Events
16.2.7.3	Adverse Events that Led to Study Drug Discontinuation
16.2.8.1	Best Corrected Visual Acuity
16.2.8.2	Best Corrected Visual Acuity - Subjects Who Lost Three or More Lines from Baseline
16.2.9.1	Biomicroscopy
16.2.9.2	Biomicroscopy - Measures with a Criterion Change
16.2.10.1	Dilated Ophthalmoscopy
16.2.10.2	Dilated Ophthalmoscopy - Subjects with a Criterion Change
16.2.10.3	Cup-to-Disc Ratio
16.2.10.4	Cup-to-Disc Ratio - Subjects with a Clinically Significant Increase
16.2.11	Vital Signs
16.2.12.1	Clinical Chemistry Results
16.2.12.2	Hematology Results
16.2.12.3	Urinalysis and Urine Microscopic Results
16.2.12.4	Urine Pregnancy Test for Females with Childbearing Potential
16.2.13	Visual Function Questionnaire (VFQ-25)
16.2.14	Contrast Sensitivity
16.3.1	Subject Disposition – Observational Period
16.3.2	Demographics and Baseline Characteristics – Observational Period
16.3.3.1	Adverse Events – Observational Period
16.3.3.2	Serious Adverse Events – Observational Period
16.3.3.3	Adverse Events that Led to Study Drug Discontinuation – Observational Period
16.3.4	Visual Function Questionnaire (VFQ-25) – Observational Period
16.3.5	Best Corrected Visual Acuity – Observational Period
16.3.6	Contrast Sensitivity – Observational Period

16.3.7	Cornea Verticillata Grading – Observational Period

23. Figures

Figure Number	Title	Population
14.2.7	Mean +/- SE of Study Eye Intraocular Pressure (mmHg) by Treatment Group, Visit, and Time Point – MCMC Multiple Imputations Intent-to-Treat Population	Intent-to-Treat Population
14.2.8.1	Mean (SD) of Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Treatment Group and Visit – MCMC Multiple Imputations Intent-to-Treat Population	Intent-to-Treat Population
14.2.8.2	Mean (SD) Change from Baseline of Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Treatment Group and Visit – MCMC Multiple Imputations Intent-to-Treat Population	Intent-to-Treat Population
14.2.8.3	Mean (SD) Percent Change from Baseline of Study Eye Mean Diurnal Intraocular Pressure (mmHg) by Treatment Group and Visit – Observed Data Intent-to-Treat Population	Intent-to-Treat Population
14.4.7.5	Kaplan-Meier Curve for Time to Cornea Verticillata Resolution/Stabilization in Study Eye by Treatment Group and Overall Netarsudil-Treated Subjects Cornea Verticillata Safety Population	Safety Population
14.4.7.6	Kaplan-Meier Curve for Time to Cornea Verticillata Resolution/Stabilization in Fellow Eye by Treatment Group and Overall Netarsudil-Treated Subjects Cornea Verticillata Safety Population	Safety Population