

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

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# STATISTICAL ANALYSIS PLAN

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

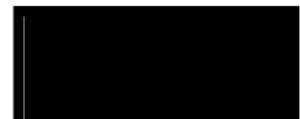
Sponsor: Aerie Pharmaceuticals, Inc.

Protocol Number: AR-13324-CS206

Author:   
  


Date: 5 February 2018

Version: 1.0



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**Statistical Analysis Plan Approval**

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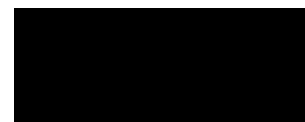
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## List of Abbreviations

AE	Adverse Event
AHD	Aqueous Humor Dynamics
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Reports
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
EVP	Episcleral Venous Pressure
HR	Heart Rate
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRB	Institutional Review Board
IP	Investigational Product
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
mmHg	Millimeters Mercury
NCS	Not Clinically Significant
OHT	Ocular Hypertension
PDF	Portable Document Format
POAG	Primary Open-Angle Glaucoma
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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-CS206, version Amendment 1 dated 16Aug2017.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (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 (CSR).

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 CSR.

## 2. Study Objectives

The primary objective of this study is to evaluate the effect on trabecular outflow facility of Netarsudil Ophthalmic Solution 0.02%, compared to Placebo, in subjects with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

The secondary objectives are: (i) to evaluate the effect on intraocular pressure (IOP) and episcleral venous pressure (EVP) of Netarsudil Ophthalmic Solution 0.02% compared to Placebo in subjects with POAG or OHT; (ii) to evaluate the ocular and systemic safety of Netarsudil Ophthalmic Solution 0.02%.

### 2.1 Primary Variables

The primary efficacy variable for the study is trabecular (tonographic) outflow facility.

### 2.2 Secondary Variables

The secondary efficacy variables include the following:

- IOP
- EVP

### 2.3 Safety Variables

The assessment of safety will be evaluated by:

- Ocular signs and symptoms /Adverse Events (AE)
- Visual Acuity (VA)
- Biomicroscopy of anterior segment including evaluation of cornea, conjunctiva, and anterior chamber



- Ophthalmoscopy
- Pachymetry and Gonioscopy (screening only)
- Heart rate (HR) and blood pressure

## 2.4 Statistical Hypotheses

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

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

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

## 3. Study Design and Procedures

### 3.1 General Study Design

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

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

Both eyes must qualify for the study with an unmedicated (post-washout or treatment-naïve) IOP of >20 mmHg but <30 mmHg at 08:00 hours and >17 mmHg but <30 mmHg at 13:00 and 16:00 hours at the qualification visit. In order to be randomized into the study, eligible subjects must meet all of the

inclusion, and none of the exclusion criteria at both the screening and at the qualification visit, following washout from their current ocular hypotensive treatment, if required.

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

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

### 3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

Day (D)/Week(W)/Month(M)	Screening	Qualification/Day 1			Exit/Day 8		
Visit	1	2/Baseline <sup>7</sup>			3/On-drug <sup>7</sup>		
Hour	--	08:00	13:00	16:00	08:00	13:00	16:00
Informed Consent	X						
Inclusion/Exclusion	X	X	X	X			
Demography	X						
Medical/Ophthalmic History	X						
HR/BP	X	X			X		
Pregnancy test <sup>1</sup>	X						
Ocular symptoms/AEs <sup>2</sup>	X	X			X		
VA (ETDRS)	X	X			X		
IOP	X	X	X	X	X	X	X
Biomicroscopy	X	X			X		
Gonioscopy <sup>3</sup>	X						
Pachymetry <sup>3</sup>	X						
Ophthalmoscopy (dilated)	X						

Eye-Drop Instillation Evaluation	X						
EVP <sup>4</sup>	X <sup>6</sup>		X	X		X	X
Tonography			X	X		X	X
Study meds dispensed				X			
Study meds instilled <sup>5</sup>					X		
Study meds collected					X		
Study completed							X

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

#### 4. Study Treatments

##### 4.1 Method of Assigning Subjects to Treatment Groups

Enrolled subjects will receive both investigational products (IPs), Netarsudil Ophthalmic Solution 0.02% (QD AM) and Placebo (QD AM). Individual eyes will be randomized to receive active treatment or Placebo; one treatment will be dosed in the right eye (OD), and the other treatment will be dosed in the left eye (OS). Each IP dose will be self-administered by the study subjects. For subjects deemed unable to self-administer the doses at the qualification visit (Visit 2, Day 1), a guardian or caregiver will be asked to administer the medication.

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

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

The randomization schedule will be provided to the investigational site. The eligible subjects will be assigned a randomization number at the end of Visit 2, Day 1. Randomization numbers will be assigned sequentially to subjects in the order in which they become eligible for randomization. The site staff will dispense to the subject the study kit labeled with the corresponding randomization number. Each kit will contain one bottle of each product labeled “right eye” (OD) and “left eye” (OS). The randomization number will be recorded on the subject's source document and electronic case report form (eCRF).

## 5. Sample Size and Power Considerations

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

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

## 6. Data Preparation

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

All 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; and
- Randomized treatment codes have been unmasked.



## **7. Analysis Populations**

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

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

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

### **7.2 Per Protocol**

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

### **7.3 Safety**

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

## **8. General Statistical Considerations**

### **8.1 Unit of Analysis**

The unit of analysis in this study will be the study eye for all ocular assessments. Both eyes are study eyes as each subject receives Active treatment in one eye and Placebo in the fellow eye. Non-ocular assessments will be presented at the subject level.

### **8.2 Missing or Inconclusive Data Handling**

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

### **8.3 Definition of Baseline**

Baseline values for all AHD (trabecular outflow facility, IOP, EVP) are the time-relevant measures at 13:00 and 16:00 hour time points on Day 1, Visit 2 (e.g., measurement at 13:00 hours at Visit 2 will be the baseline for the measurement at 13:00 hours on Day 8, Visit 3).

Baseline mean diurnal values for all AHD is defined as the average of 13:00 and 16:00 hour measurements on Day 1, Visit 2.

#### **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, visit, and time point (as applicable) based on all randomized subjects unless otherwise specified.

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

All study data entered in the database will be listed by subject, visit, and time point (as applicable).

All statistical tests will be performed with a significance level of 5% (one-tailed). Where applicable, two-sided 90% and 95% CIs will be reported.

#### **8.5 Adjustments for Multiplicity**

No adjustments for multiplicity are planned.

### **9. Disposition of Subjects**

The following disposition items will be summarized:

- The number and percentage of subjects in each analysis population
- The number and percentage of subjects who completed the study
- The number and percentage of subjects who withdrew from the study and the reasons for premature discontinuation
- The number and percentage of subjects with any major deviations

All percentages will use the number of subjects treated as the denominator, unless indicated otherwise.

In addition, subject disposition and protocol deviation listings will be provided.

### **10. Demographic and Pretreatment Variables**

#### **10.1 Demographic Variables**

The demographic variables collected in this study include age, gender, race, and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for all randomized subjects.

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:

$$\text{Age} = (\text{informed consent date} - \text{date of birth}) / 365.25 \text{ truncated as an integer}$$

The number and percentage of subjects will be presented, for age category, gender, race, and ethnicity.

A subject listing that includes all demographic variables will be provided.

## **10.2 Pretreatment Variables**

Ophthalmoscopy (dilated) examination (Retina, Vitreous, Macula, Choroid, Optic nerve; graded as normal or abnormal and cup-disc ratio) will be conducted at screening only.

Central corneal thickness (µm) will be measured by ultrasound pachymetry in both eyes (mean of two readings per eye). The mean value will be used for enrollment criteria. Pachymetry within 1 week of screening are acceptable.

Gonioscopy will be performed to confirm that the iridocorneal angle is open, and that the subject does not have narrow angle glaucoma, which is an exclusion criteria for study participation. Gonioscopy may be taken up to three months (i.e., within 90 days) prior to enrollment of the subject.

Subject listings will be produced for ophthalmoscopy, pachymetry, and gonioscopy results.

## **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.

A listing of medical history will be generated.

### **11.2 Concomitant Medications**

Concomitant medications that are taken within 30 days prior to screening and during the study will be recorded in the CRF. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, (Enhanced B2, March 2017) 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. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Concomitant medications will be summarized for all randomized subjects. Medications will be tabulated for all subjects if non-ocular and for each treatment if ocular using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

## **12. Dosing Compliance and Treatment Exposure**

### **12.1 Dosing Compliance**

A subject listing of study drug administration (i.e., showing whether subject used study eye drops for all seven days or not) will be produced.

## **13. Efficacy Analyses**

All efficacy analyses will be conducted using the mITT population. If mITT is different from PP population, then the analyses will be repeated for the PP population.

### **13.1 Primary Analysis**

The primary efficacy endpoint is the mean change from baseline in mean diurnal trabecular outflow facility (average of 13:00 and 16:00 hour measurements) per treatment on Day 8. Baseline mean diurnal outflow facility is defined as the average of 13:00 and 16:00 hour measurements on Day 1, Visit 2.

The null and alternative hypotheses, based on the primary endpoint, are as follow:

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

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

The null hypothesis will be tested using a paired t-test with  $\alpha=0.05$ . One-sided p-values, two-sided 90% confidence intervals (CI), and two-sided 95% CIs will be presented. The trabecular outflow facility will be summarized by treatment and visit/time point using continuous descriptive statistics ( and listed by subject.

### **13.2 Secondary Analyses**

The secondary efficacy endpoints include:



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

Mean change from baseline in mean diurnal IOP and EVP will be analyzed similarly to the primary endpoint.

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

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

All secondary efficacy endpoints will be summarized by treatment and visit/time point using continuous descriptive statistics.

#### **14. Exploratory Analyses**

Not applicable.

#### **15. Safety Analyses**

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, will be documented on the respective eCRF. AEs will be

documented from the time the subject receives the first dose of IP until the subject's participation in the study has been completed; therefore all AEs collected on the eCRFs are treatment-emergent AEs (TEAEs)

All TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 to identify system organ class (SOC) and preferred term (PT).

An overall summary will be presented that includes the number and percentage of subjects who experienced at least one TEAE. This summary will also include breakdowns of TEAEs further categorized as ocular (AR-13324, Placebo; Subjects with AEs reported in both eyes will be counted in both treatments) or non-ocular, serious TEAEs (SAEs), TEAEs by maximum relationship, TEAEs by maximum severity, TEAEs leading to subject withdrawal, and TEAEs leading to death.

In addition, separate summaries will be provided for the following categories of TEAEs:

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

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

Separate summaries will also be provided for the following categories of TEAEs:

- TEAEs by Relationship
- TEAEs by Severity

Treatment-emergent AEs will be summarized by maximum relationship to study drug and maximum severity. Relationship to drug will be scored by Investigator as Not Related, Unlikely Related, Possibly

Related, and Related. Related AEs will be classified as those scored as Possibly Related and Related. Severity will be rated by the Investigator as Mild, Moderate, Severe, Life Threatening, Death. All percentages will use the number of safety subjects as the denominator. Summary tables will include the number and percentage of subjects experiencing at least one TEAE in each SOC, PT, and grouping, relationship or severity. If a subject experiences more than 1 AE within SOC or PT, that subject will be counted only once for that event under the maximum severity or most related category for the study drug. Similarly, in the event that relationship or severity data are missing, the study analysis will follow the assumption of maximum relationship or severity in the summary tables. The tabular summaries will be sorted by descending order of overall incidence.

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

### **15.2 Visual Acuity (ETDRS)**

Visual Acuity (VA) is taken at all visits as a measure of ocular function. VA will be measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

The observed and change from baseline in VA, in Logarithm of the Minimum Angle of Resolution (logMAR) units, will be summarized using continuous descriptive statistics by visit for each treatment. The proportion of subjects with different ranges of worsening from baseline, including those of  $\geq 3$  lines ( $\geq 0.3$  logMAR), will also be summarized. A subject listing of VA will also be produced.

### **15.3 Slit-Lamp Biomicroscopy Examination**

A slit-lamp biomicroscopy examination of the conjunctiva, cornea, anterior chamber, lid, iris/pupil, and lens will be performed at each visit. The results will be graded as none (0), mild (+1), moderate (+2), severe (+3), and Hypopyon (+4, applies to anterior chamber cells only), except for lens status and iris/pupil.

The results will be summarized using counts and percentages for each treatment at each visit. Percentages will be based on the number of subjects in each treatment with responses.

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

A subject listing of the slit-lamp biomicroscopy parameters, including positive findings noted by investigators, will also be produced.

### **15.4 Vital Signs**

Vital signs will be summarized with continuous descriptive statistics at each visit. A subject listing of the vital signs results will also be produced.

No laboratory testing is planned for this study, other than pregnancy testing for females of child-bearing potential. Pregnancy results will be listed by subject.

Not applicable.

There are no changes from the protocol-stated analyses.

However, there are changes in the devices for measuring some of the AHD measures; trabecular outflow facility will be measured using Berkeley Bio-Engineering Tonography or V. Mueller Tonography, and IOP will be measured using a Pneumatonometer (Model 30 Classic, Reichert Inc., Buffalo, NY). These changes will be reflected in footnotes for the tables and listings.

None.

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

Tables that will be included in the topline delivery are shown in boldface font.

[illegible]

[illegible]

## 21. Listings

[illegible]

## 22. Figures

None.